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(54) Title: CYCLIC PEPTIDE ANTIFUNGAL AGENTS		
(57) Abstract The present invention provides phosphorylating agents and phosphorylation conditions that are compatible with the acid- and base-sensitive compounds and which promote a regioselective and reproducible conversion to a phosphonate compound. Also provided are intermediates that may be used to prepare phosphonate derivatives of cyclic peptides antifungal agent and a process for converting the phosphonates to the desired phosphonic acid prodrugs.		

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CYCLIC PEPTIDE ANTIFUNGAL AGENTS

FIELD OF THE INVENTION

The present invention is in the field of organic chemistry. Specifically, the present invention provides phosphonylating agents and conditions that may be used to prepare phosphonate derivative.

BACKGROUND OF THE INVENTION

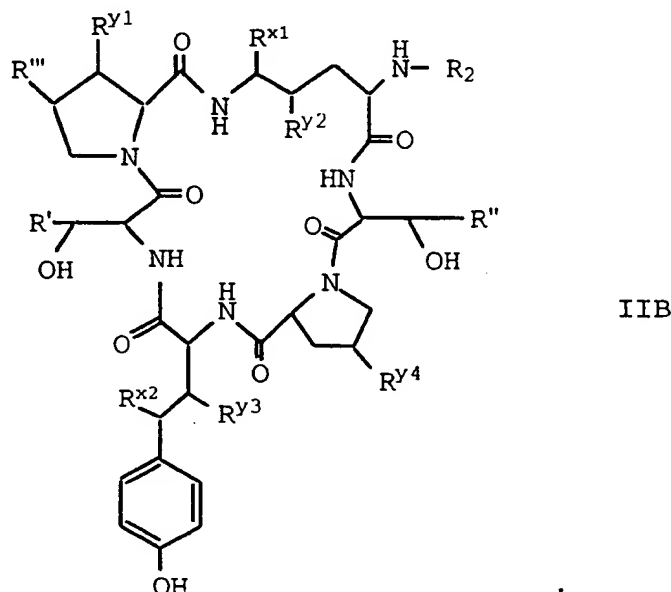
This invention relates to a phosphonylating agent and phosphonylation conditions that are mild and promote a regioselective, reproducible conversion of an hydroxy moiety to the corresponding phosphonate derivative. The phosphonylating agents and conditions may be used for preparing derivatives of pharmaceutical compounds which have improved stability and water solubility. For example, this invention may be used to make derivatives of various cyclic peptide compounds which are used as antifungal and antiparasitic agents.

In general, the cyclic peptides are unstable under basic conditions. Specifically, the presence of a base causes ring opening and decomposition of the cyclic peptide. In addition, the cyclic peptides are sensitive to strong acids. A popular strategy for phosphonylating the hydroxy moiety of a compound involves the use of an alkyl phosphonic dichloride as the phosphonylating agent. However, a by-product of the hydrolytic work-up of the reaction is hydrochloric acid. The reaction is typically carried out in the presence of a base which both promotes the phosphonylation reaction and acts as an acid scavenger. This reaction has limited usefulness with respect to the cyclic peptides as a result of poor yields due to the sensitivity of the nucleus to both base and acid. In addition, alkyl phosphonic dichloride reagents are very reactive and not regioselective for reaction at only the desired phenolic oxygen of the polyfunctional cyclic peptides.

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The cyclic peptides are produced by fermentation of various microorganisms. A number of cyclic peptides are known in the art including echinocandin B (A30912A), aculeacin, mulundocandin, sporiofungin, L-671,329, and S31794/F1. In general, these cyclic peptides may be structurally characterized as a cyclic hexapeptide core (or nucleus) with an acylated amino group on one of the core amino acids. The amino group is typically acylated with a fatty acid group forming a side chain off the nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain. The fatty acid side chains may be removed from the cyclic peptide core to provide an amino nucleus (for example, a compound of formula II, below, where R₂ is hydrogen). The amino group may then be re-acylated to provide semi-synthetic compounds which may be phosphorylated according to the present invention.

Examples of echinocandin compounds that may be converted to the corresponding phosphonate derivatives include compounds of formula IIB:



- 3 -

wherein:

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;

R'' and R''' are independently methyl or hydrogen;

$\text{R}^{\text{x}1}$, $\text{R}^{\text{x}2}$, $\text{R}^{\text{y}1}$, $\text{R}^{\text{y}2}$, $\text{R}^{\text{y}3}$, and $\text{R}^{\text{y}4}$ are independently

5 hydroxy or hydrogen; and

R_2 is an acyl side chain as defined herein.

Such cyclic peptides are useful antifungal and antiparasitic agents due to their biological activity against these pathogens. These compounds may be used as
10 oral, topical or intravenous (iv) drugs. However, these compounds are not well-suited for intravenous formulation due to their relatively poor aqueous solubility. Yet, an iv formulation is particularly desirable when the drug is to be used with a patient who is unable to take it orally,
15 for example because the patient is immunocompromised, or when it is necessary to obtain high levels of compound systemically, for example when treating a systemic infection, an organ infection such as hepatosplenic infection or an iv catheter candida infection.

20 The development of an antifungal or antiparasitic drug using these compounds necessitates increasing the aqueous solubility of the compounds using either formulation technology or by the development of a suitable prodrug. With respect to the latter, it has been discovered that the
25 phosphonic acid derivatives of the various cyclic peptides have properties that are desirable for effective prodrugs. Specifically, the echinocandins may be converted to a phosphonic acid prodrug by phosphorylating the phenolic hydroxy of the homotyrosine moiety and then deprotecting
30 the resultant phosphonate to provide the desired phosphonic acid derivative.

The present invention provides a phosphorylating agent and phosphorylation conditions that are compatible with the sensitive cyclic peptide nucleus and promote a clean and
35 reproducible conversion to a phosphonate derivative. The

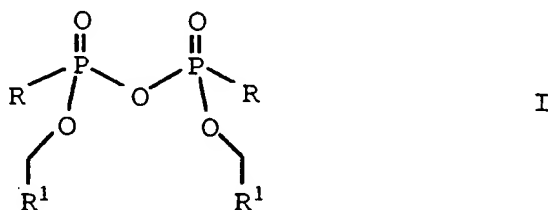
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phosphonylation conditions are selective for phosphonylation at the homotyrosine moiety.

The present invention also provides intermediate compounds useful in preparing the phosphonate derivatives of these cyclic peptides and a process for preparing the desired phosphonic acid derivatives.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I:



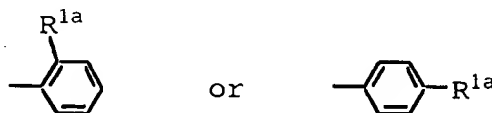
where:

R is C₁-C₆ alkyl, phenyl or benzyl;

R¹ is phenyl, naphthyl, cyclohexyl or a compound of the formula



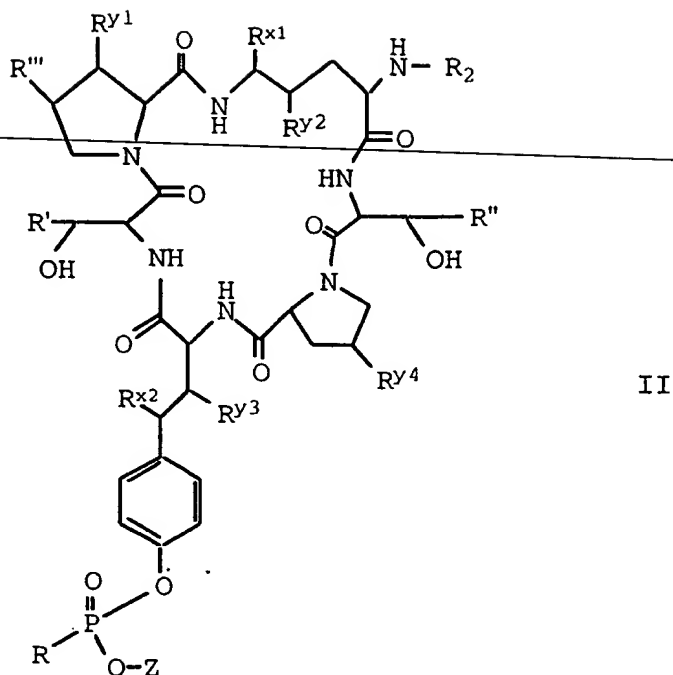
where R^{1a} is hydrogen, halo, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl or benzyloxy; with the proviso that when R¹ is



then R^{1a} cannot be hydroxy, C₁-C₆ alkoxy or benzyloxy; or a pharmaceutically acceptable salt thereof.

Also provided is a compound of formula II

- 5 -



wherein:

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;

5 R'' and R''' are independently methyl or hydrogen;

$\text{R}^{\text{x}1}$, $\text{R}^{\text{x}2}$, $\text{R}^{\text{y}1}$, $\text{R}^{\text{y}2}$, $\text{R}^{\text{y}3}$, and $\text{R}^{\text{y}4}$ are independently hydroxy or hydrogen;

R is C_1 - C_6 alkyl, phenyl or benzyl;

Z is $-\text{CH}_2-\text{R}^1$;

10 R¹ is phenyl, naphthyl, cyclohexyl or a compound of the formula

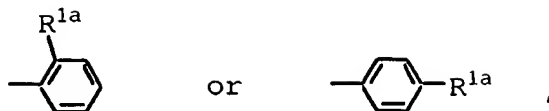


where R^{1a} is hydrogen, halo, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl or benzyloxy;

15 R₂ is acyl;

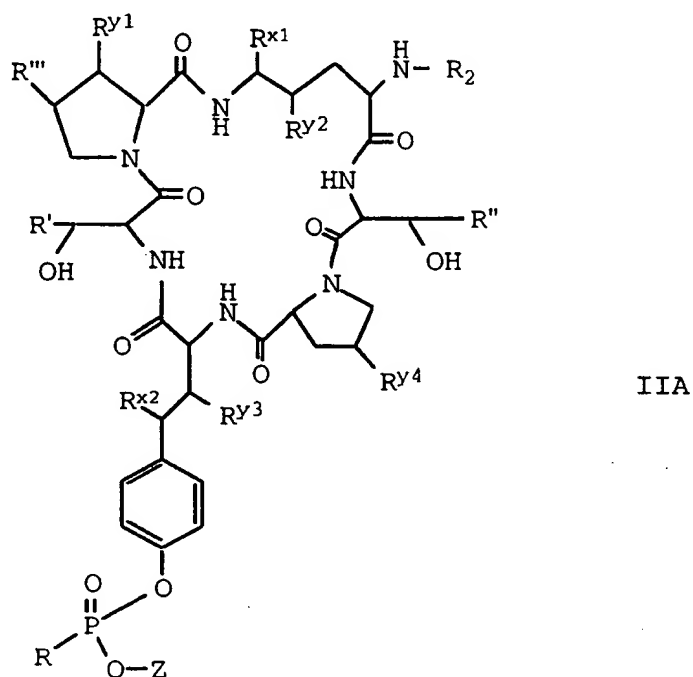
with the proviso that when R¹ is

- 6 -



then R^{1a} cannot be hydroxy, $\text{C}_1\text{-C}_6$ alkoxy or benzyloxy;
 or a pharmaceutically acceptable salt thereof.

- 5 The present invention further provides a process for
 preparing a compound of formula IIA



wherein:

- 10 R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2\text{-}$;
 R'' and R''' are independently methyl or hydrogen;
 R^{x1} , R^{x2} , R^{y1} , R^{y2} , R^{y3} , and R^{y4} are independently
 hydroxy or hydrogen;
 R is $\text{C}_1\text{-C}_6$ alkyl, phenyl or benzyl;
 15 Z is hydrogen or $-\text{CH}_2\text{-R}^1$;
 R^1 is phenyl, naphthyl, cyclohexyl or a compound of
 the formula

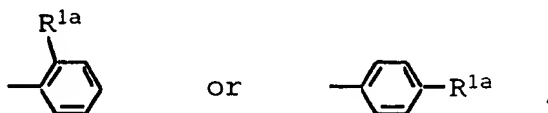
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where R^{1a} is hydrogen, halo, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl or benzyloxy;

5 R_2 is acyl;

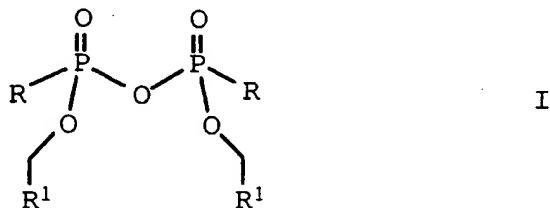
with the proviso that when R^1 is



then R^{1a} cannot be hydroxy, C_1 - C_6 alkoxy or benzyloxy; or a pharmaceutically acceptable salt thereof;

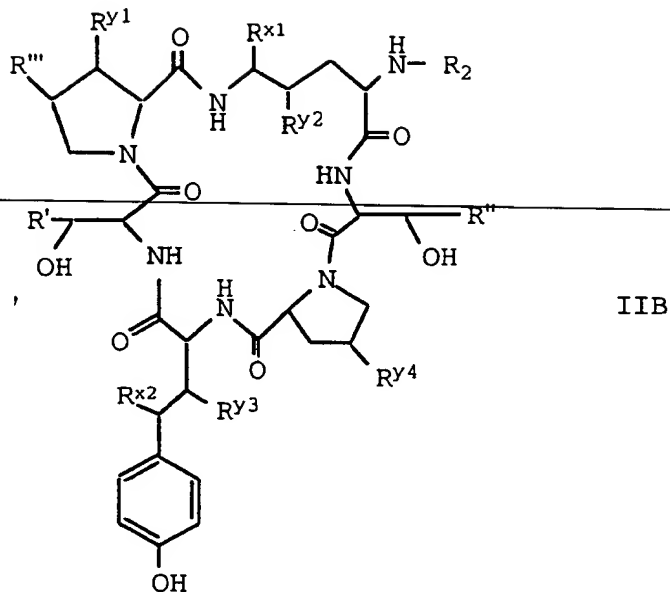
10 which comprises

a) reacting a compound of formula I



15 with a compound of formula IIB

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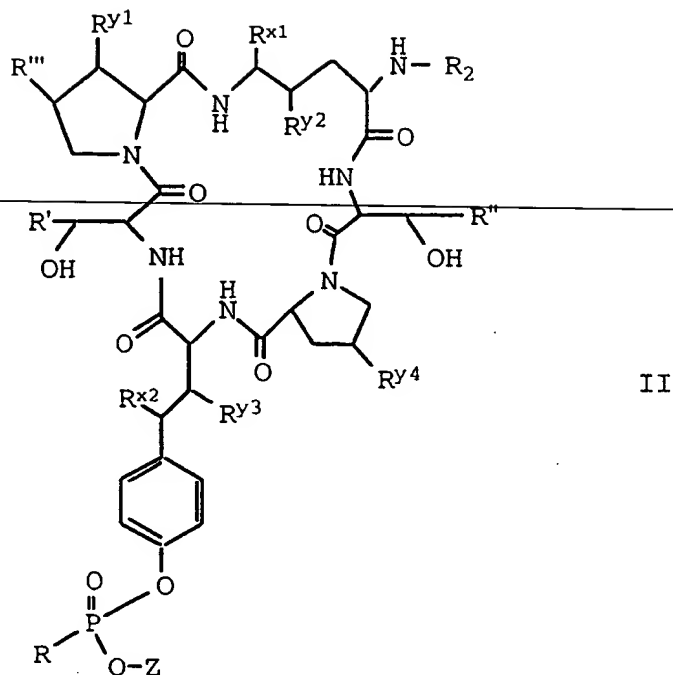
in the presence of a base at a temperature of from about
-30°C to about 40°C to provide a compound of formula II;

5 b) optionally converting the compound of formula II to
provide the compound of formula IIA where Z is hydrogen;
and

c) optionally forming a pharmaceutically acceptable
salt.

10 The present invention further provides a process for
converting a compound of formula II:

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wherein:

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;

R'' and R''' are independently methyl or hydrogen;

5 RX^1 , RX^2 , RY^1 , RY^2 , RY^3 , and RY^4 are independently hydroxy or hydrogen;

R is C_1 - C_6 alkyl, phenyl or benzyl;

Z is $-\text{CH}_2-\text{R}^1$;

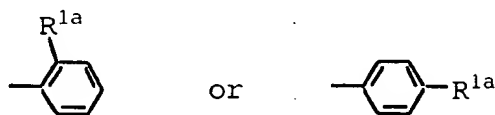
10 R^1 is phenyl, naphthyl, cyclohexyl or a compound of the formula



where R^{1a} is hydrogen, halo, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl or benzyloxy;

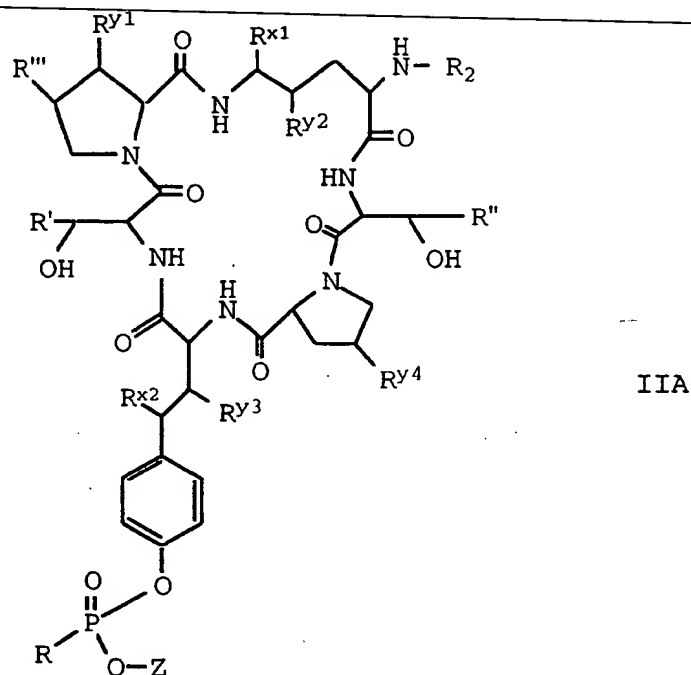
15 R_2 is acyl;

with the proviso that when R^1 is



- 10 -

then R^{1a} cannot be hydroxy, C₁-C₆ alkoxy or benzyloxy;
 or a pharmaceutically acceptable salt thereof;
 to a compound of formula IIA:



5

where:

R', R'', R''', R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4}, R and R₂ are as defined above; and

Z is hydrogen,

10

which comprises

1) hydrogenating the compound of formula II by

a) exposure to hydrogen gas in the presence of a catalyst and a base; or

b) reaction with an alkali metal in liquid ammonia; and

15

2) optionally forming a pharmaceutically acceptable salt.

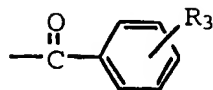
DETAILED DESCRIPTION

As used herein, the term "acyl" refers to the substituent, R₂ in a compound of formula II, above:

20

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I) R_2 is a group of the formula:

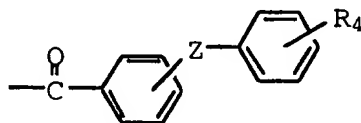


where:

- 5 A) R_3 is C_1 - C_{12} alkyl, C_1 - C_6 alkoxy or quinolyl;
 B) R_3 is $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$;
 m and n are independently 2, 3 or 4;
 p is 0 or 1; or
 C) R_3 is $-Y-(C_1-C_{12} \text{ alkyl})$;
 10 Y is $-C\equiv C-$ or $-CH=CH-$; or
 D) R_3 is $-O-(CH_2)_q-G$;
 q is 2, 3 or 4;
 G is C_7 - C_{10} bicycloalkyl or C_7 - C_{14}

tricycloalkyl; or

15 II) R_2 is a group of the formula:



where:

- Z is $-O-$, $-C\equiv C-$, $-CH=CH-$, $-CH_2-CH_2-$, $-CH_2-$ or a bond;
 20 A) R_4 is hydrogen, C_1 - C_{12} alkyl, C_1 - C_{12} substituted
 alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} substituted alkenyl, C_2 - C_{12}
 alkynyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy, C_3 - C_{12}
 cycloalkyl, C_7 - C_{10} bicycloalkyl, C_7 - C_{14} tricycloalkyl,
 C_3 - C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl,
 25 benzothienyl, quinolyl or phenyl; or
 B) R_4 is phenyl substituted by amino, C_1 - C_{12}
 alkylthio, halo, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12}
 alkynyl, C_1 - C_{12} substituted alkyl, C_2 - C_{12} substituted
 30 alkenyl, C_2 - C_{12} substituted alkynyl, C_1 - C_{12} alkoxy,

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trifluoromethyl, phenyl, substituted phenyl, or phenyl substituted with a group of the formula
-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl) where m, n and p are as defined above; or

5

C) R₄ is C₁-C₁₂ alkoxy substituted with halo, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₁-C₆ alkoxy, C₂-C₁₂ alkynyl, amino, C₁-C₄ alkylamino, di(C₁-C₄ alkyl)amino, formamido, C₂-C₁₂ alkanoylamino, or
10 phenyl substituted with a group of the formula
-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl) where m, n and p are as defined above; or

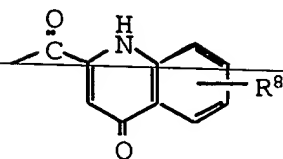
D) R₄ is -O-(CH₂)_r-W-R₅;
15 r is 2, 3 or 4;
W is pyrrolidino, piperidino or piperazino;
R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or

E) R₄ is -Y¹-R₆;
Y¹ is -C≡C- or -CH=CH-;
R₆ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl
25 substituted with C₁-C₁₂ alkylthio, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, halo(C₁-C₆ alkoxy) or a group of the formula
-O-(CH₂)_r-W-R₅ where r, W and R₅ are as defined above; or
R₆ is phenyl substituted with a group of the
formula -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl) where m, n and
30 p are as defined above; or

F) R₄ is C₁-C₁₂ alkoxy substituted with a group of the formula -NHC(O)R₇;
R₇ is C₁-C₆ alkoxy, or phenyl(C₁-C₆ alkoxy); or

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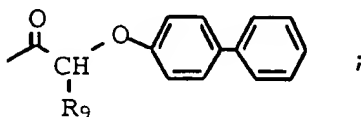
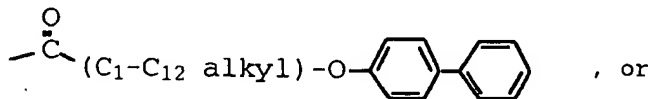
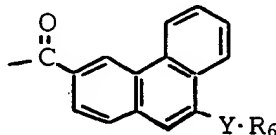
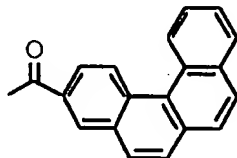
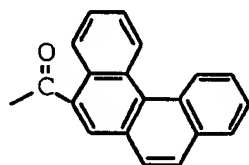
III) R_2 is a group of the formula



5 where R^8 is C_1 - C_{12} alkoxy or a group of the formula
 $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m , n and p are
 as defined above; or

IV) R_2 is a group of the formula

10



where:

Y and R_6 are as defined above;

15 R_9 is phenyl, C_1 - C_{12} alkyl, or C_1 - C_{12} alkoxy; or

V) R₂ is naphthoyl substituted with R₄ where R₄ is as defined above.

The term "C₁-C₁₂ alkyl" refers to a straight or
5 branched alkyl chain having from 1 to 12 carbon atoms.
Typical C₁-C₁₂ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 5-methylpentyl, hexyl, heptyl, 3,3-dimethylheptyl, octyl, 2-methyl-octyl, nonyl, decyl, undecyl, dodecyl and the like.
10 The term "C₁-C₁₂ alkyl" includes within its definition the terms "C₁-C₆ alkyl" and C₁-C₄ alkyl."

The term "halo" refers to chloro, fluoro, bromo or iodo.

15 The term "C₂-C₁₂ alkenyl" refers to a straight or branched alkenyl chain having from 2 to 12 carbon atoms. Typical C₂-C₁₂ alkenyl groups include ethenyl, 1-propen-2-yl, 3-buten-1-yl, 1-buten-2-yl, 1-buten-1-yl, 1-penten-3-yl, 2-hexen-3-yl, 1-decen-2-yl, 2-decen-5-yl and the like.

20 The term "C₂-C₁₂ alkynyl" refers to a straight or branched alkynyl chain having from 2 to 12 carbon atoms. Typical C₂-C₁₂ alkynyl groups include ethynyl, 1-propyn-1-yl, 1-propyn-2-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-pentyn-3-yl, 4-pentyn-2-yl, 1-hexyn-3-yl, 3-hexyn-1-yl, 5-methyl-3-hexyn-1-yl, 5-octyn-1-yl, 7-octyn-1-yl, 4-decyn-1-yl, 6-decyn-1-yl and the like.
25

The term "C₁-C₁₂ alkylthio" refers to a straight or branched alkyl chain having from 1 to 12 carbon atoms attached to a sulfur atom. Typical C₁-C₁₂ alkylthio groups
30 include methylthio, ethylthio, propylthio, isopropylthio, butylthio, 3-methyl-heptylthio, octylthio, 5,5-dimethyl-hexylthio and the like.

The term "C₁-C₁₂ alkoxy" refers to a straight or branched alkyl chain having from 1 to 12 carbon atoms
35 attached to an oxygen atom. Typical C₁-C₁₂ alkoxy groups

- 15 -

include methoxy, ethoxy, propoxy, butoxy, sec-butoxy, pentoxy, 5-methyl-hexoxy, heptoxy, octyloxy, decyloxy dodecyloxy and the like. The term "C₁-C₁₂ alkyl" includes within its definition the terms "C₁-C₆ alkoxy" and "C₁-C₄ alkoxy."

The terms "C₁-C₁₂ substituted alkyl," "C₂-C₁₂ substituted alkenyl" and "C₂-C₁₂ substituted alkynyl," refers to the specified moiety substituted with 1 or 2 substituents independently selected from halo, hydroxy, protected hydroxy, amino, protected amino, C₁-C₇ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino, phenyl, substituted phenyl or C₁-C₁₂ alkoxy.

The term "substituted phenyl" refers to a phenyl group substituted with 1, 2 or 3 substituents independently selected from halo, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, carboxy, protected carboxy, carboxymethyl, hydroxymethyl, amino, aminomethyl, trifluoromethyl or N-methylsulfonylamino.

The term "C₃-C₁₂ cycloalkyl" refers to a saturated hydrocarbon ring structure having from 3 to 12 carbon atoms. Typical C₃-C₁₂ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cyclooctyl and the like.

The term "C₃-C₁₂ cycloalkoxy" refers to a C₃-C₁₂ cycloalkyl group attached to an oxygen atom. Typical C₃-C₁₂ cycloalkoxy groups include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy and the like.

The term "C₃-C₁₂ cycloalkenyl" refers to a hydrocarbon ring structure having from 3 to 12 carbon atoms with at least one double bond. Typical C₃-C₁₂ cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

The term "methyl(C₃-C₁₂ cycloalkyl)" refers to a

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C₃-C₁₂ cycloalkyl group that is substituted with a methyl group. Typical methyl(C₃-C₁₂ cycloalkyl) groups include 2-methylcyclopropyl, 2-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl and the like.

5 The term "C₁-C₄ alkylamino" refers to a straight or branched alkylamino chain having from 1 to 4 carbon atoms attached to a nitrogen atom. Typical C₁-C₄ alkylamino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and the like.

10 The term "di(C₁-C₄ alkyl)amino" refers to a di(C₁-C₄ alkyl)amino chain having two straight or branched alkyl chains of from 1 to 4 carbon atoms attached to a common nitrogen atom. Typical di(C₁-C₄ alkyl)amino groups include dimethylamino, diethylamino, ethylmethylamino, methylisopropylamino, dipropylamino, dibutylamino, methylbutylamino, t-butylisopropylamino, di-t-butylamino and the like.

15 The term "C₂-C₁₂ alkanoyl" represents a straight or branched alkyl chain having from 1 to 4 carbon atoms attached to a carbonyl moiety. Typical C₂-C₁₂ alkanoyl groups include ethanoyl, propanoyl, isopropanoyl, butanoyl, isobutanoyl, sec-butanoyl, t-butanoyl, pentanoyl and the like.

20 The term "C₂-C₁₂ alkanoylamino" represents a straight or branched alkyl chain attached to a carbonylamino moiety. Typical C₂-C₁₂ alkanoylamino groups include ethanoylamino, propanoylamino, isopropanoylamino, butanoyl-amino, isobutanoylamino, sec-butanoylamino, t-butanoylamino, pentanoylamino and the like.

25 The terms "C₇-C₁₀ bicycloalkyl" represents two fused cycloalkyl rings having a total of 7 to 10 carbon atoms and "C₇-C₁₄ tricycloalkyl" represents 3 fused cycloalkyl rings having a total of 7 to 14 carbon atoms. Typical "C₇-C₁₀ bicycloalkyl" and "C₇-C₁₄ tricycloalkyl" groups include bicyclo[2.2.1.]hept-2-yl, bicyclo[2.2.1.]hept-4-en-2-yl,

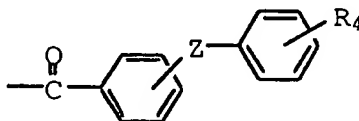
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bicyclo[3.3.1.]non-3-yl, bicyclo[3.3.1.]non-2-yl, bicyclo[3.2.1.]oct-2-yl, bicyclo[2.2.2.]oct-2-yl, bicyclo[2.2.2.]oct-5-en-2-yl, adamantyl and the like.

Preferred acyl groups, R_2 , include groups of the
5 formula:



wherein:

Z is $-C\equiv C-$, $-CH=CH-$, $-CH_2-CH_2-$, or a bond;

10 **A)** R_4 is hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} alkynyl, C_2-C_{12} substituted alkynyl, C_1-C_{12} alkoxy, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl, C_3-C_{12} cycloalkoxy, naphthyl, pyridyl, thienyl,
15 benzothienyl, quinolyl or phenyl; or

B) R_4 is phenyl substituted by amino, C_1-C_{12} alkylthio, halo, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} substituted alkyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} substituted alkynyl, C_1-C_{12} alkoxy,
20 trifluoromethyl, phenyl, substituted phenyl, or a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

C) R_4 is C_1-C_{12} alkoxy substituted with halo, C_3-C_{12} cycloalkyl, C_7-C_{10} bicycloalkyl, C_7-C_{14} tricycloalkyl,
25 C_1-C_6 alkoxy, C_2-C_{12} alkynyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, formamido, C_2-C_{12} alkanoylamino, or phenyl substituted with a group of the formula $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$ where m, n and p are as defined above; or

30 **D)** R_4 is $-O-(CH_2)_r-W-R_5$;
 r is 2, 3 or 4;
 W is pyrrolidino, piperidino or piperazino;

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R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or

E) R₄ is -Y¹-R₆;

Y¹ is -C≡C- or -CH=CH-;

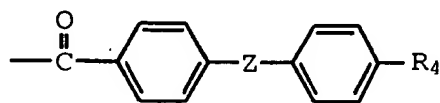
5 ~~R₆ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl,~~
 C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, or phenyl substituted with C₁-C₁₂ alkylthio, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, halo(C₁-C₆ alkoxy) or a group of the formula
 10 -O-(CH₂)_r-W-R₅ where r, W and R₅ are as defined above; or

R₆ is phenyl substituted with a group of the formula -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl) where m, n and p are as defined above; or

F) R₄ is C₁-C₁₂ alkoxy substituted with a group of
 15 the formula -NHC(O)R₇;

R₇ is C₁-C₆ alkoxy, or phenyl(C₁-C₆ alkoxy).

More preferred are acyl groups, R₂, of the formula:



20 where Z is -C≡C- or a bond;
 or a pharmaceutically acceptable salt thereof.

The following acyl groups, R₂, are preferred:

- 20 -

allyl, trimethylsilyl, (t-butyl)dimethylsilyl, and 2,2,2-trichloroethoxycarbonyl and the like. The species of hydroxy protecting group is not critical so long as the derivatized hydroxy group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. A preferred hydroxy-protecting group is trimethylsilyl. Further examples of hydroxy-protecting groups are described in T.W. Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., (2nd ed., 1991) chapters 2 and 3. The term "protected hydroxy" refers to a hydroxy group bonded to one of the above hydroxy-protecting groups.

The term "dideoxy" refers to compounds of the formula IIB where R^{X1} and R^{X2} are each hydrogen.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate,

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butyne-1,4-dioate, hexyne-1,6-dioate, benzoate,
chlorobenzoate, methylbenzoate, dinitrobenzoate,
hydroxybenzoate, methoxybenzoate, phthalate, sulfonate,
xylenesulfonate, phenylacetate, phenylpropionate,

5 phenylbutyrate, citrate, lactate, γ -hydroxybutyrate,
glycollate, tartrate, methanesulfonate, propanesulfonate,
naphthalene-1-sulfonate, naphthalene-2-sulfonate,
mandelate and the like. Preferred pharmaceutically
acceptable acid addition salts are those formed with
10 mineral acids such as hydrochloric acid and hydrobromic
acid, and those formed with organic acids such as maleic
acid and methanesulfonic acid.

Base addition salts include those derived from
inorganic bases, such as ammonium or alkali or alkaline
15 earth metal hydroxides, carbonates, bicarbonates, and the
like. Such bases useful in preparing the salts of this
invention thus include sodium hydroxide, potassium
hydroxide, ammonium hydroxide, potassium carbonate, sodium
carbonate, sodium bicarbonate, potassium bicarbonate,
20 calcium hydroxide, calcium carbonate and the like. The
potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion
forming a part of any salt of this invention is not of a
critical nature, so long as the salt as a whole is
25 pharmacologically acceptable and as long as the counterion
does not contribute undesired qualities to the salt as a
whole.

Preferred compounds of formula I are those compounds
where:

30 R is C₁-C₄ alkyl;

R¹ is phenyl or a compound of the formula



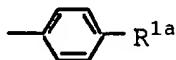
where R^{1a} is hydrogen, halo, C₁-C₆ alkyl or C₁-C₆ alkoxy;
or a pharmaceutically acceptable salt thereof.

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Of these compounds, more preferred compounds of formula I are those compounds where:

R is methyl;

5 ~~R¹ is phenyl or a compound of the formula~~

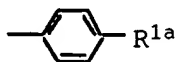


where R^{1a} is halo or hydrogen;
or a pharmaceutically acceptable salt thereof.

10

Further preferred compounds are those compounds of formula I where:

R¹ is phenyl or a compound of the formula

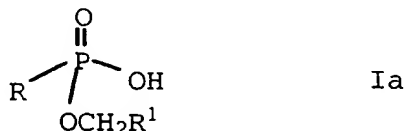


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where R^{1a} is bromo or hydrogen;
or a pharmaceutically acceptable salt thereof.

The compounds of formula I may be prepared by self-coupling the corresponding phosphonic acid of formula Ia

20



where R¹ is defined in claim 1, in an aprotic solvent at a temperature of from about 0°C to about 60°C and in the presence of a coupling agent.

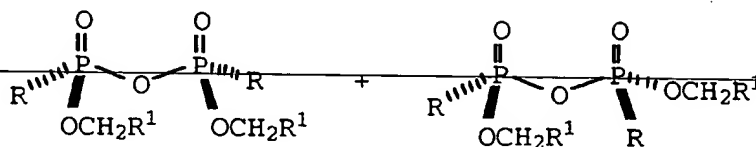
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The phosphonic acid Ia is inherently racemic due to the following tautomeric equilibrium:



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When the tautomers are coupled, they provide a mixture of syn and anti diastereomers:



5

The reaction is typically carried out for about 30 minutes to about 24h at a temperature of from about 15°C to about 40°C, preferably for about 30 minutes to about 2h at room temperature. Typical solvents for this reaction include aprotic solvents such as tetrahydrofuran (THF), ethyl acetate (EtOAc), toluene or methylene chloride (CH₂Cl₂) or a mixture of such solvents. A preferred solvent mixture is one formed from EtOAc and CH₂Cl₂, preferably in a ratio of 5:1 of EtOAc to CH₂Cl₂. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. Typical coupling agents include dicyclohexylcarbodiimide (DCC), N,N'-carbonyldiimidazole, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP) and the like. A preferred coupling agent is DCC.

25

The pyrophosphonates prepared in the coupling reaction described above are obtained as a mixture of syn and anti diastereomers. The diastereomers may be separated using procedures known in the art. For example, they may be separated by selective recrystallization from a suitable solvent or solvent mixture. A preferred solvent mixture is a mixture of hexanes and EtOAc. Either diastereomeric form or the diastereomeric mixture may be used as a phosphorylating agent.

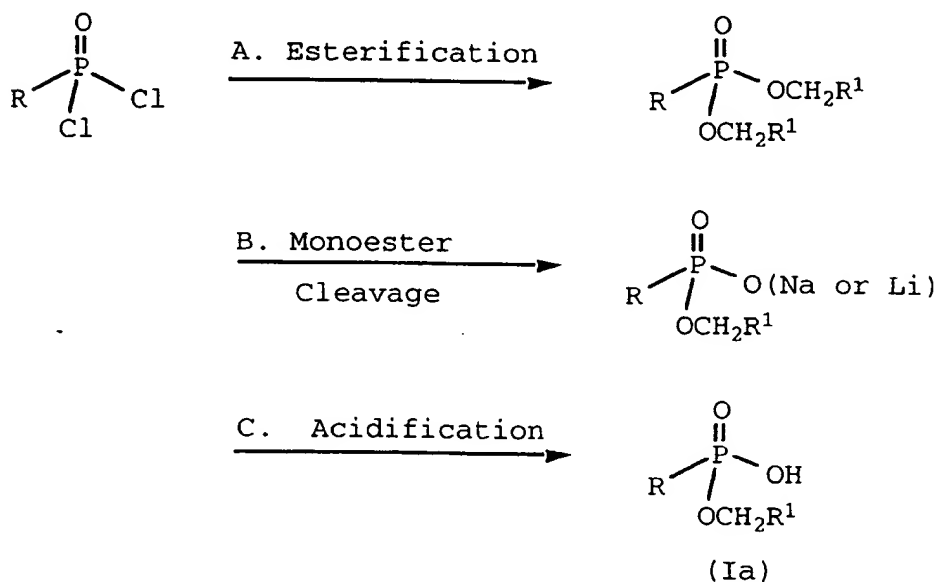
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The pyrophosphonate compounds, the mixture of pyrophosphonate diastereomers or any of the intermediate compounds used to prepare such pyrophosphonates may be isolated by procedures well-known in the art. For example, once a reaction is complete, the desired compound may be crystallized and then collected by filtration, or the reaction solvent may be removed by evaporation or decantation. The desired compound may also be isolated from the reaction mixture by extraction. The intermediate compound may be further purified, if desired, by common techniques such as crystallization or chromatography over solid supports such as silica gel, alumina and the like, before carrying out the next step of the reaction scheme.

The compounds of formula Ia may be prepared according to Reaction Scheme I, as follows.

Reaction Scheme I



Reaction scheme I, above, is accomplished by carrying out reactions A-C, in order.

In reaction IA, a suitably substituted phosphonic acid dihalide is esterified by reaction with an appropriately substituted alcohol, preferably in the presence of a base.

- 25 -

Preferred phosphonic acid dihalides used in this reaction are the dichlorides. The reaction is typically carried out with 2-4 equivalents of the alcohol relative to the phosphonic acid dihalide at a temperature of from about -

5 40°C to about 25°C. Suitable solvents for this reaction include solvents such as THF, diethyl ether (Et₂O), methyl-

t-butylether (MTBE) or CH₂Cl₂, preferably Et₂O or MTBE. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants

10 are sufficiently solubilized to effect the desired reaction. Typical bases include triethylamine (Et₃N), N-methyl-morpholine (NMM) and diisopropylethylamine. A preferred base is diisopropylethylamine in the presence of a catalytic amount of 1H-tetrazole. The reaction is

15 generally complete in about 3 to 5 hours when carried out at a temperature of from about 0°C to about 25°C.

In reaction IB, one of the ester groups on the diester compound obtained from reaction IA is selectively cleaved by reaction with sodium iodide (NaI) or lithium iodide

20 (LiI) in a suitable solvent to provide the corresponding monoester compound. The reaction is typically carried out with 1 to 3 equivalents of the iodide relative to the diester compound at a temperature of from about -20°C to the reflux temperature of the mixture. Suitable solvents

25 for this reaction include solvents such as acetone, dimethylformamide (DMF), EtOAc, CH₂Cl₂ and the like. A preferred solvent is acetone. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently

30 solubilized to effect the desired reaction.

In reaction IC, the monoester compound obtained from reaction IB is converted to the desired phosphonic acid Ia by treatment with an aqueous acid. Typical acids include any inorganic acid such as HCl, hydrobromic acid or

35 sulfuric acid. A preferred acid is HCl. The acid is

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typically used in a concentration of about 0.1 molar (0.1M) to about 12M, preferably about 6M.

An alternate synthesis of the phosphonic acid Ia is by direct monochloride displacement of a phosphonic acid
5 dihalide with a suitably substituted alcohol of the formula

R^1-CH_2OH at a temperature of from about $-40^{\circ}C$ to about $25^{\circ}C$ in a suitable organic solvent such as THF, Et_2O , MTBE or CH_2Cl_2 . The reaction is preferably carried out in the presence of a base. The reaction is generally carried out
10 with an equimolar amount to about a two times excess of the phosphonic acid dihalide relative to the alcohol. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction.
15 Typical bases include, Et_3N , N-methylmorpholine (NMM), diisopropylethylamine or 1H-tetrazole. The reaction is generally complete in about 90 minutes when carried out at a temperature in the range of $0-5^{\circ}C$.

The reaction may be quenched by the addition of water
20 and a base such as an hydroxide such as sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), or Et_3N , diisopropylethylamine or NMM which results in a mixture of the desired pyrophosphonate and the corresponding phosphonic acid monoester Ia. Since some
25 phosphonic diester is formed in the reaction mixture, it is preferable to hydrolyze the pyrophosphonate to the corresponding phosphonic monoester by stirring the pyrophosphonate for about 8 to about 36h in the presence of
30 an aqueous base to hydrolyze the pyrophosphonate compound to the phosphonic acid monoester Ia (such as is isolated above in Reaction IC). Typical bases include the hydroxides such as NaOH, KOH, LiOH or calcium hydroxide. The desired phosphonic acid Ia may be easily separated from the phosphonic acid diester by extraction.

35 The naturally-occurring cyclic peptides used in the present invention may be prepared by fermentation of known

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microorganisms. For example, the cyclic peptide of formula IIB where R', R" and R''' are methyl, R^{x1} and R^{x2} are hydroxy, RY¹, RY², RY³, RY⁴ are hydroxy and R₂ is linoleoyl (cyclic peptide corresponding to A-30912A) may be prepared using

5 the procedure detailed in Abbott et al., U.S. Pat. Ser. No. 4,293,482, which is herein incorporated by reference. The

nucleus of formula IIB where R', R", and R''' are methyl, R^{x1} is hydroxy, R^{x2} is hydrogen, RY¹, RY², RY³, RY⁴ are hydroxy and R₂ is linoleoyl (nucleus corresponding to A-30912B) may

10 be prepared using the procedure detailed in Abbott et al., U.S. Pat. Ser. No. 4,299,763, which is herein incorporated by reference. The cyclic peptide of formula IIB where R', R", and R''' are methyl, R^{x1} and R^{x2} are hydrogen, RY¹, RY³ and RY⁴ are hydroxy, RY² is hydrogen and R₂ is linoleoyl

15 (nucleus corresponding to A-30912D) may be prepared using the procedure detailed in Abbott et al., U.S. Pat. Ser. No. 4,299,762, which is herein incorporated by reference.

Aculeacin may be prepared using the procedure detailed in Mizuno et al., U.S. Pat. Ser. No. 3,978,210 which is herein

20 incorporated by reference. The cyclic peptide of formula IIB where R' is -CH₂C(O)NH₂, R" is methyl, R''' is hydrogen, R^{x1}, R^{x2}, RY¹, RY³, RY⁴ are hydroxy may be prepared using the procedure detailed in U.S. Pat. Ser. No. 5,021,341, which is herein incorporated by reference.

25 The dideoxy compounds of formula IIB are prepared by removing the benzylic and aminor hydroxy groups (R^{x2} and R^{x1}, respectively). The hydroxy groups may be removed by subjecting a non-dideoxy compound of formula IIB (where R₂ is hydrogen or acyl) to a strong acid and a reducing agent

30 at a temperature of between -5°C and 70°C, in a suitable solvent. Typical strong acids include trichloroacetic acid, trifluoroacetic acid or boron trifluoride etherate. A preferred strong acid is trifluoroacetic acid. Typical reducing agents include sodium cyanoborohydride or

35 triethylsilane. A preferred reducing agent is

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triethylsilane. Suitable solvents include CH₂Cl₂, chloroform or acetic acid, preferably CH₂Cl₂. The strong acid is present in an amount of from 2 to 60 mol per mol of substrate, and the reducing agent is present in an amount of 2 to 60 mol per mol of substrate. This process affords selective removal of the ainal and benzylic hydroxy groups.

The semi-synthetic cyclic peptides of formula IIB may be prepared by deacylating the naturally occurring cyclic peptides using procedures known in the art to provide the corresponding amino nucleus (compound of formula IIB where R₂ is hydrogen). This reaction is typically carried out enzymatically, by exposing the naturally occurring cyclic peptide to a deacylase enzyme. The deacylase enzyme may be obtained from the microorganism Actinoplanes utahensis and used substantially as described in U.S. Patent Nos. 4,293,482 and 4,304,716, herein incorporated by reference. The deacylase enzyme may also be obtained from the Pseudomonas species. Deacylation may be accomplished using whole cells of Actinoplanes utahensis or Pseudomonas or the crude or purified enzyme thereof or using an immobilized form of the enzyme. See European Patent Application No. 0 460 882 (December 11, 1991). Examples of naturally-occurring cyclic peptides which may be used as starting materials include aculeacin (palmitoyl side chain), tetrahydroechinocandin B (stearoyl side chain), mulundocandin (branched C₁₅ side chain), L-671,329 (C₁₆ branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C₁₅ branched side chain), FR901379 (palmitoyl side chain) and the like. A preferred naturally-occurring cyclic peptide is echinocandin B (compound of formula IIB where R', R'', and R''' are each methyl, R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} are each hydroxy, and R₂ is linoleoyl).

The amino nucleus is then re-acylated using procedures known in the art to provide a compound of formula II where

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R₂ is a semi-synthetic acyl group. For example, the amino nucleus may be acylated by reaction with an appropriately substituted acyl halide, preferably in the presence of an acid scavenger such as a tertiary amine, such as Et₃N. The reaction is typically carried out at a temperature of from about -20°C to about 25°C. Typical solvents for this reaction include polar aprotic solvents such as dioxane or DMF. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction.

The amino nucleus may also be acylated by reaction with an appropriately substituted carboxylic acid, in the presence of a coupling agent. Typical coupling agents include DCC, N,N'-carbonyldiimidazole, BOP-Cl, EEDQ, PyBOP and the like.

In addition, the amino nucleus may be acylated with an activated ester of a carboxylic acid (RCOOH) such as an ester of a carboxylic acid of the formula R₂-COOH and p-nitrophenyl, 2,4,5-trichlorophenyl, hydroxybenzotriazole hydrate (HOBT·H₂O), pentafluorophenol, N-hydroxysuccinimide and the like. Preferred acylating moieties are the active esters of the carboxylic acid R₂-COOH such as 2,4,5-trichlorophenyl ester and HOBT ester. The reaction is typically carried out for about 1-65 hours at a temperature from about 0°C to about 30°C in an aprotic solvent. The reaction is generally complete after about 24-48 hours when carried out at a temperature of from about 15°C to about 30°C. Typical solvents for this reaction are THF and DMF or a mixture of such solvents. The amino nucleus is generally employed in equimolar proportions or with a slight excess of the amino nucleus relative to the activated ester.

The cyclic peptides are phosphonylated by reaction with the pyrophosphonate in the presence of a base. Typical bases include LiOH, sodium hydride, Et₃N, NMM, lithium trimethylsilanolate (LiOTMS), lithium t-butoxide

- 30 -

(*t*-BuOLi), lithium bis(trimethylsilyl)amide (LHMDS), pyridine and the like. A preferred base is LiOtBu. The reaction is typically carried out for about 15 minutes to about 6h at a temperature of from about -30°C to about 40°C in a suitable solvent. Suitable solvents include THF, DMF, dimethylacetamide, 1,2-dimethoxyethane, dimethylsulfoxide (DMSO) and the like. The reaction is generally complete in about 30 minutes to about 3h when carried out under these conditions. The pyrophosphonate reactant is generally employed in equimolar proportions to about a one mol excess relative to the cyclic peptide in the presence of an equimolar or slight excess of the base. Phosphonylation of a cyclic peptide with unprotected aminor hydroxy groups (R^{x1} and R^{x2}) is typically carried out at a temperature from about -30°C to about -15°C due to the sensitivity of the nucleus to the base whereas phosphonylation of a cyclic peptide with protected aminor hydroxy groups or a dideoxy cyclic peptide can be carried out at slightly higher temperatures.

The phosphonylated cyclic peptide is readily converted to the corresponding phosphonic acid derivative using conditions known in the art. For example, the phosphonate compounds may be catalytically hydrogenated by exposure to 1-3 atmospheres of hydrogen gas (H_2) in the presence of a catalyst such as palladium or platinum on a solid support and in the presence of a base such as Et_3N , NMM, pyridine, diisopropylethylamine or the like, in a suitable solvent such as THF, DMF or a THF/DMF mixture. A preferred base is Et_3N . A preferred catalyst is palladium-on-carbon (Pd/C). Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactant is sufficiently solubilized to effect the desired reaction. The reaction is generally substantially complete after about 1 to 24 hours when conducted at a temperature of from about 0°C to about 40°C. The reaction is preferably conducted at a temperature of from about 20°C to about 30°C

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for about 2 to 5 hours. Alternatively, the phosphonylated cyclic peptide may be converted by chemical hydrogenation such as exposure to an alkali metal in liquid ammonia.

5 The amination hydroxy groups on the cyclic peptide may be optionally protected with an hydroxy-protecting group using procedures known in the art. For example, the cyclic peptide is reacted with a suitable hydroxy-protecting group in the presence of a catalyst at a temperature in the range of from about 0°C to about 40°C for about 1 to 5 hours in a
10 mutual inert solvent. The hydroxy-protecting group is generally employed in an amount ranging from about equimolar proportions to about a 100 molar excess relative to the cyclic peptide, preferably in a large molar excess. Suitable catalysts include strong acids such as p-
15 toluenesulfonic acid, camphorsulfonic acid (CSA), hydrochloric acid (HCl), sulfuric acid, trifluoroacetic acid (CF₃COOH) and the like. Typical solvents suitable for use in this reaction include any organic solvent such as dioxane. Solvent choice is not critical so long as the
20 solvent employed is inert to the ongoing reaction and/or the reactants are sufficiently solubilized to effect the desired reaction. The reaction is preferably conducted at a temperature in the range of from about 20°C to about 30°C for about 2 to 4 hours. It is not necessary to protect the
25 dideoxy compounds of formula II. After phosphonylating the protected cyclic peptide, the hydroxy-protecting groups may be removed according to procedures known in the art. For example, the protecting groups can be removed by reaction with a Lewis acid in a mutual inert organic solvent such as
30 CH₂Cl₂. Examples of Lewis acids include trimethylsilyl bromide, boron trifluoride etherate and the like. The reaction is typically carried out at a temperature of from about 0°C to about 40°C, preferably from about 20°C to about 30°C. A preferred Lewis acid is boron trifluoride
35 etherate.

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The R₂-COOH precursor acids are prepared by hydrolyzing a nitrile of the formula R₂-CN or an ester of the formula

R₂-COO(C₁-C₄ alkyl). The nitrile and ester intermediates
5 may be prepared using procedures known in the art.

For example, the nitrile and ester intermediates where R₂ is an alkoxy aryl moiety may be prepared using Procedure A or Procedure B, described below.

Procedure A

10 One equivalent of an alkyl bromide, iodide, or p-toluenesulfonate is added to a mixture containing one equivalent of a base, such as potassium t-butoxide or potassium carbonate (K₂CO₃), and one equivalent of an hydroxy aryl compound in 200-300mL of acetonitrile (CH₃CN).

15 The reaction mixture is refluxed for 6h and then concentrated in vacuo to provide a residue which is dissolved in a Et₂O/2N NaOH mixture. The resulting layers are separated and the organic layer is dried over magnesium sulfate (MgSO₄), filtered and dried to provide the alkoxy
20 aryl product.

Procedure B

Diethylazodicarboxylate (1 equiv.) is added dropwise to a mixture containing an hydroxy aryl compound (1 equiv.), an alkyl alcohol (1 equiv.) and triphenylphosphine
25 (1 equiv.) in 200-300mL of THF. After 17h, the solvent is removed in vacuo to provide a residue which is dissolved in Et₂O. The resulting mixture is washed with a 2N NaOH solution, dried over MgSO₄, filtered and concentrated to provide a product which is then crystallized from a
30 Et₂O/pentane mixture or, if the product contains a tertiary amine, the hydrochloride salt is formed and crystallized from a methanol (MeOH)/EtOAc mixture.

The nitrile and ester intermediates where R₂ is an alkynyl or alkenyl aryl moiety may be prepared using
35 Procedure C, below.

- 33 -

Procedure C

A mixture containing Et₂O (2 equiv.), palladium dichloride (0.05 equiv.), triphenylphosphine (0.1 equiv.), cuprous iodide (0.025 equiv.) and an alkyne (1 equiv.) or an alkene (2 equiv.) is added to one equivalent of an aryl bromide, iodide, or trifluoromethanesulfonate in CH₃CN (600mL/0.1mol of aryl reactant), under nitrogen (N₂). The resulting mixture is refluxed for 17h and then the solvent is removed in vacuo to provide a residue which is slurried in 300mL of Et₂O and then filtered. The filtrate is washed with a 1N HCl solution, dried over MgSO₄, filtered and then dried to provide the product.

The ester intermediates where R₂ is a terphenyl moiety may be prepared using Procedure D, below.

Procedure D1. Formation of boronic acid reactant

Butyl lithium (1.2 equivalents) is added to one equivalent of a cold (-78°C) aryl halide in THF. After 15 minutes, triisopropyl borate (2 equiv.) is added. After 10 minutes, the reaction mixture is warmed to room temperature and quenched by the addition of water (H₂O), followed by the addition of 1N HCl. The resulting layers are separated and the organic layer is concentrated in vacuo to provide a solid which is collected by filtration and washed with hexane.

2. Formation of terphenyl ester

Tetrakis(triphenylphosphine)palladium (0.03 equiv.) is added to a mixture containing an aryl boronic acid (1 equiv.), K₂CO₃ (1.5 equiv.) and methyl 4-iodobenzoate (1 equiv.) (or trichlorophenyl ester of iodobenzoate) in N₂-purged toluene. The reaction mixture is refluxed for 7h and then decanted to remove the K₂CO₃ and dried in vacuo to provide a residue. This residue is triturated in CH₃CN and filtered to provide the product.

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The aryl nitriles and esters described above may be converted to the corresponding carboxylic acids by hydrolysis using Procedure E or Procedure F, below.

Procedure E

5 An aryl nitrile is dissolved in ethanol (EtOH) and an excess of 50% NaOH solution and refluxed for 2h. Water is added to the reaction mixture until a solid precipitates. This solid is collected by filtration, added to a dioxane/6N HCl mixture and the resulting mixture is
10 refluxed for 17h. When the reaction is substantially complete, the carboxylic acid product is crystallized by the addition of H₂O and then collected by filtration and dried in vacuo.

Procedure F

15 An excess of 2N NaOH is added to an aryl ester in MeOH, and the resulting solution is refluxed for 5h and then acidified by the addition of excess HCl. Water is added to the reaction mixture until a solid (carboxylic acid) precipitates. The carboxylic acid is collected by
20 filtration and dried in vacuo.

 The carboxylic acids may be converted to the corresponding 2,4,5-trichlorophenyl esters using Procedure G, below. These activated esters are then used to acylate the amino nucleus, as described above in Reaction Scheme
25 IC:

Procedure G

 A mixture containing an aryl carboxylic acid (1 equiv.), 2,4,5-trichlorophenol (1 equiv.) and DCC (1 equiv.) in CH₂Cl₂ is stirred for 17h and then filtered. The
30 filtrate is concentrated to provide a residue which is dissolved in Et₂O, filtered, and then pentane is added until crystallization begins. The crystals are collected by filtration and dried in vacuo.

 Alternatively, the carboxylic acid may be activated by
35 conversion to the corresponding hydroxybenzotriazole ester using Procedure H, below.

- 35 -

Procedure H

An aryl carboxylic acid (1 equiv.) and a slight excess of N-mesylate substituted hydroxybenzotriazole (1.2 equiv.) were reacted in the presence of a slight excess of a base such as triethylamine (Et₃N) (1.3 equiv.) in DMF, under N₂.

When the reaction was complete, the mixture was diluted with toluene and washed with H₂O. The organic portion was diluted with H₂O and then filtered using t-butyl methyl ether (MTBE) for transferring the material. The resultant solid was washed with MTBE and then dried in vacuo.

The present invention may be used to phosphonylate any hydroxy groups, for example in alcohols and phenols. The phosphonylation agents described herein are particularly useful for phosphonylating hydroxy functions in compounds that have acid-sensitive functional groups. The alcohols may be obtained from commercial sources or prepared according to procedures known in the art.

The following Preparations and Examples further describe how to synthesize the compounds of the present invention. The terms melting point, proton nuclear magnetic resonance spectra, mass spectra, infrared spectra, ultraviolet spectra, elemental analysis, high performance liquid chromatography, and thin layer chromatography are abbreviated "m.p.", "NMR", "MS", "IR", "UV", "Analysis", "HPLC", and "TLC", respectively. In addition, the absorption maxima listed for the IR spectra are only those of interest and not all of the maxima observed.

In addition, examples of the phosphonylation of various alcohols are provided to demonstrate the selective phosphonylation of an alcohol in a polyfunctional system and the ability to use the mild conditions with compounds having sensitive functionalities.

In conjunction with the NMR spectra, the following abbreviations are used: "s" is singlet, "d" is doublet, "dd" is doublet of doublets, "t" is triplet, "q" is quartet, "m" is multiplet, "dm" is a doublet of multiplets and "br.s", "br.d", "br.t", and "br.m" are broad singlet,

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doublet, triplet, and multiplet respectively. The symbol "J" indicates the coupling constant in Hertz (Hz). Unless otherwise noted, NMR data refers to the free base of the subject compound. The NMR spectra were obtained on a
5 General Electric QE-300 300 MHz instrument or a Bruker AC300 300 MHz instrument. The chemical shifts are expressed in delta (δ) values (parts per million downfield from tetramethylsilane).

10

Preparation 1

A. Di-(4-bromobenzyl) methylphosphonate

A cold (0°C) solution of 4-bromobenzyl alcohol (22g, 117.6mmol) and 1H-tetrazole (0.34g, 4.85mmol) in Et₂O (300mL), was treated with diisopropylethylamine (24mL, 137.8mmol), followed by the dropwise addition of
15 methylphosphonic dichloride (8.7g, 65.45mmol) (which was added while maintaining a temperature of 0-3.5°C). After stirring at 0°C for 30 minutes, the mixture was warmed to room temperature and allowed to react for an additional 4h
20 which resulted in the formation of a precipitate. The reaction was monitored using TLC (90:10 CH₂Cl₂/EtOAc). The precipitate was removed by suction filtration and then rinsed with Et₂O (3 X 50mL). The resultant filtrate was concentrated in vacuo and then redissolved in 10mL of
25 CH₂Cl₂, filtered through a sintered glass funnel of silica gel (68g, packed with CH₂Cl₂) and then eluted using 95:5 CH₂Cl₂/EtOAc.

Yield: 22.7 g (89%)

TLC: R_f 0.43 (9:1 CH₂Cl₂/EtOAc).

30

IR (CHCl₃): 3420, 3005, 1596, 1490, 1408 cm⁻¹.

¹H NMR (CDCl₃): δ 1.47 (d, 1H, J=17.65 Hz), 4.94 (m, 4H),
7.19 (d, 4H, J=8.29 Hz), 7.46 (d, 4H, J=8.31 Hz).

¹³C NMR (DMSO-d₆): δ 9.63, 11.48, 65.35, 65.43, 121.21,
129.7, 131.27, 136.01, 136.09.

35

MS(FD⁺): m/z 434.

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Analysis for $C_{15}H_{15}BrO_3P$:

Calcd: C, 41.51; H, 3.48; Br, 36.82;

Found: C, 41.31; H, 3.34; Br, 37.21.

5

B. Sodium 4-bromobenzyl methylphosphonate

A mixture of Preparation 1A (17g, 39.16mmol) and NaI (11.7g, 78.06mmol) in anhydrous acetone (20mL) was refluxed for 5h, resulting in the formation of a precipitate. When the reaction was substantially complete, as indicated by

10 TLC (90:10 CH_2Cl_2 /EtOAc), the mixture was cooled to room temperature and suction filtered. The precipitate was slurried in acetone (20mL) and then filtered to provide a yellow solid which was rinsed with acetone (4 x 30mL) and then dried in vacuo.

15 Yield: 10 g of a white solid (88.9%).

IR ($CHCl_3$): 1489, 1307, 1281 cm^{-1} .

1H NMR (D_2O): δ 1.29 (d, 3H, $J=16.41$ Hz), 4.87 (d, 2H, $J=7.29$ Hz), 7.36 (d, 2H, $J=8.31$ Hz), 7.59 (d, 2H, $J=8.38$ Hz).

20 MS(FAB⁺): m/z 287.

Analysis for $C_8H_9BrNaO_3P$:

Calcd: C, 33.48; H, 3.16;

Found: C, 33.71; H, 3.11.

25

C. 4-Bromobenzyl methylphosphonic acid

A cold (0°C) solution of Preparation 1B (7g, 24.38mmol) in THF (35mL) was treated dropwise with 6M HCl (4.2mL, 25.2mmol). After removing the cooling bath, the mixture was stirred for 10 minutes resulting in the

30 formation of a precipitate which was removed by filtration. The filtrate was concentrated in vacuo to provide a solid. This solid was redissolved in CH_2Cl_2 (75mL), dried over sodium sulfate (Na_2SO_4), filtered and then dried in vacuo to provide 6.8 g of a white solid (96.3% UV pure using HPLC).

35 This solid was redissolved in warm EtOAc (25mL) and filtered through a fritted disc. The filtrate was

- 38 -

concentrated in vacuo to half the volume and diluted with hexanes which resulted in the precipitation of a white powder. This powder was collected by filtration, washed with 80:20 hexanes/EtOAc and dried in vacuo.

5 Yield: 5.5 g.

~~HPLC showed 99% UV purity.~~

Spectral data was consistent with the material prepared in Preparation 4.

10

Preparation 2

A. Dibenzyl methylphosphonate

The compound was prepared substantially in accordance with the procedure detailed in Preparation 1A.

TLC: R_f 0.36 (9:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$).

15

IR (CHCl_3): 3673, 3415, 3036, 1498, 1456, 1312, 1238 cm^{-1} .

^1H NMR (CDCl_3): δ 1.46 (d, 3H, $J=17.65$ Hz), 5.00 (m, 4H), 7.34 (s, 10H).

^{13}C NMR ($\text{DMSO}-d_6$): δ 9.74, 11.60, 66.17, 66.25, 127.69, 128.09, 128.40, 136.62, 136.70.

20

MS(FD^+): $M^+ = 277$.

B. Sodium benzyl methylphosphonate

The compound was prepared substantially in accordance with Preparation 1B using Preparation 2A, with the exception that the desired compound was extracted from the reaction mixture after acidification (due to contamination with the disodium salt).

25

^1H NMR (D_2O): δ 1.31 (d, 3H, $J=16.35\text{Hz}$), 4.92 (d, 2H, $J=7.08\text{Hz}$), 7.45 (m, 5H).

30

C. Benzyl methylphosphonic acid

A solution of Preparation 2B (400 mg containing 20-30% of the disodium salt) in H_2O (0.5mL) was adjusted to pH 3 by the addition of 1N HCl. The resultant mixture was extracted with EtOAc (3 x 5mL) and the combined extracts

35

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were dried over Na_2SO_4 , filtered and concentrated in vacuo to provide an oil which was dried in vacuo.

Yield: 149 mg.

TLC: R_f 0.18 (8:2:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{HOAc}$).

5 IR (CHCl_3): 3600-3000, 1456, 1314 cm^{-1} .

^1H NMR (CDCl_3): δ 1.49 (d, 3H, $J=17.88$ Hz), 5.03 (d, 2H, $J=7.88$ Hz), 7.36 (m, 5H), 12.61 (br.s, 1H).

^{13}C NMR (75 MHz, CDCl_3): δ 10.85, 12.79, 66.58, 66.66, 127.80, 128.34, 128.58, 136.23, 136.32.

10 MS (FD^+): m/z 187 (MH^+).

Analysis for $\text{C}_8\text{H}_{11}\text{O}_3\text{P}$:

Calcd: C, 51.62; H, 5.96;

Found: C, 51.69; H, 5.89.

15

Preparation 3

A. Di-(4-methoxybenzyl) methylphosphonate

The compound was prepared substantially in accordance with Preparation 1A.

IR (CHCl_3): 3005, 2962, 1614, 1587, 1465, 1312, 1305, 20 1251, 1175, 1033, 1015 cm^{-1} .

^1H NMR (CDCl_3): δ 1.41 (d, 3H, $J=18$ Hz), 3.79 (s, 3H), 4.88 (dd, 2H, $J=12$ Hz, 9 Hz), 4.97 (dd, 2H, $J=12$ Hz, 9 Hz), 6.88 (d, 2H, $J=9$ Hz), 7.29 (d, 2H, $J=9$ Hz).

^{13}C NMR (CDCl_3): δ 159.76, 129.82, 128.55, 128.47, 113.95, 25 77.63, 77.20, 66.96, 66.88, 55.23, 12.75, 10.85.

MS (FD^+) $\text{M}^+ = 336$.

Analysis for $\text{C}_{17}\text{H}_{21}\text{O}_5\text{P}$:

Calcd: C, 60.71; H, 6.29;

Found: C, 60.99; H, 6.39.

30

B. Sodium 4-methoxybenzyl methylphosphonate

The compound was prepared substantially in accordance with Preparation 1B using Preparation 3A, with the

- 40 -

exception that only 1.1 equivalents of NaI were used and the reaction was run at room temperature for 16h.

Yield = 70%.

^1H NMR (D_2O): δ 1.21 (d, 3H, $J=18$ Hz), 3.79 (s, 3H), 4.79 (d, 2H, $J=8.7\text{Hz}$), 6.91 (d, 2H, $J=9.6\text{Hz}$), 7.38 (d, 2H, $J=9.6\text{Hz}$).

Analysis for $\text{C}_8\text{H}_{12}\text{O}_4\text{PNa}$:

Calcd: C, 45.39; H, 5.08;

Found: C, 46.01; H, 5.15.

Preparation 4

4-Bromobenzyl methylphosphonic acid

A solution containing 4-bromobenzyl alcohol (49.4g, 0.26mol) and Et_3N (39mL, 0.28mol) in CH_2Cl_2 (150mL) was slowly added to a cold (0°C) solution of methyl phosphonic dichloride (36.96g, 0.28mol) in 200mL of CH_2Cl_2 , under N_2 . When the reaction was substantially complete, as determined by HPLC, an additional 39mL of Et_3N was added, followed by 20mL of H_2O resulting in an exotherm up to 27°C , followed by an additional 30mL of H_2O . According to HPLC, the reaction mixture contained 55% of the compound of Preparation 6, 4.5% of the desired compound and 20% of the compound of Preparation 1A. The reaction mixture was transferred to a separatory funnel and washed with 1N HCl (2 x 150mL). The organic layer was combined with 150mL of 2N NaOH and 50mL of H_2O , stirred overnight to hydrolyze the compound of Preparation 6 to the desired compound and then separated. The aqueous layer was washed with CH_2Cl_2 (2 x 150mL), acidified with 22mL of 12N HCl and then extracted with CH_2Cl_2 (400mL). The organic extract was dried over Na_2SO_4 , filtered and then dried in vacuo to provide 53.74 g of a white solid which was suspended in EtOAc (110mL), stirred vigorously for 3h, isolated by filtration and then dried in vacuo (at 50°C).

Yield: 48.72 g (71% yield).

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IR (CHCl₃): 3600-3000, 1597, 1490, 1314 cm⁻¹.

¹H NMR (CDCl₃): δ 1.50 (d, 3H, J=18Hz), 4.97 (d, 2H, J=8Hz), 7.23 (d, 2H, J=8 Hz), 7.48 (d, 2H, J=8Hz), 12.41 (br.s, 1H).

¹³C NMR (CDCl₃): δ 10.81, 12.75, 65.75, 65.83, 122.39, 129.36, 131.74, 135.20, 135.29.

Analysis for C₈H₁₀BrO₃P:

Calcd: C, 36.25; H, 3.80;

Found: C, 36.55; H, 3.86.

Preparation 5

Benzyl methylphosphonic Acid

The compound was prepared substantially as described in Preparation 4, using benzyl alcohol.

Yield: 88%.

Preparation 6

A. Syn/anti mixture of diastereomeric di-(4-bromobenzyl) dimethylpyrophosphonate

A mixture containing Preparation 4 (70g, 261.1mmol) and DCC (24.7g, 132.8mmol) in EtOAc (700mL) and CH₂Cl₂ (140mL) was stirred for 1h and then filtered. The filtrate was dried in vacuo to provide a solid which was suspended in heptane (340mL) and stirred for 20 minutes, filtered and then dried in vacuo to provide a white solid.

Yield: 64.2 g (95% yield).

IR (CHCl₃): 3012, 1596, 1491, 1317, 1261 cm⁻¹.

¹H NMR(CDCl₃): δ 1.65 and 1.70 (d, 3H, J=18 Hz); 5.21-5.01 (m, 2H), 7.23 and 7.26 (d, 2H, J=8 Hz), 7.48 and 7.49 (d, 2H, J=8 Hz).

¹³C NMR (CDCl₃): δ 12.00, 12.05, 12.09, 13.99, 14.04, 14.09, 67.05, 67.10, 67.15, 67.19, 122.80, 129.72, 129.80, 131.86, 134.61.

MS (FD⁺): m/z 508, 509, 510, 511, 512, 513, 514, 515 for ⁷⁹Br and ⁸¹Br combinations.

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Analysis for $C_{16}H_{18}Br_2O_5P_2$:

Calcd: C, 37.53; H, 3.54;

Found: C, 37.74; H, 3.59.

5

B. syn or anti diastereomer

The mixture of diastereomers isolated in Preparation 6A was separated by recrystallization. First, the product from Preparation 6A (820 mg) was dissolved in warm EtOAc (100mL) and filtered. The filtrate was diluted with
10 hexanes (100mL) and allowed to stand at 4°C for 4 days resulting in the formation of a white precipitate which was collected by filtration and rinsed three times with 80:20 hexanes/EtOAc (3 x 10mL). The pure diastereomer thus obtained was not assigned unequivocally as the syn or anti
15 diastereomer.

Yield: 570 mg.

1H NMR ($CDCl_3$): δ 1.67 (d, 6H, $J=17.69$ Hz), 5.09 (m, 4H),
7.22 (d, 4H, $J=8.46$ Hz), 7.48 (d, 4H, $J=8.31$ Hz).

20

Preparation 7

Syn/anti-dibenzyl dimethylpyrophosphonate

To a solution of 7.37 g (39.6mmol) of Preparation 5 in 50mL of EtOAc, was added 4.1 g (19.8mmol) of DCC. The resulting slurry was stirred for 30 minutes and filtered.
25 The filtrate was evaporated to provide 7.0 g of an oil. Analysis by HPLC showed 96.3 area % product and 0.8 area % starting material. The material was used without further purification.

1H NMR ($CDCl_3$): δ 1.55-1.75 (m, 6H), 5.05-5.25 (m, 4H),
30 7.38 (m, 10H).

MS (FD+): m/z 355.

Preparation 8

A. 4-Bromo-4'-pentyloxybiphenyl

35

Anhydrous K_2CO_3 (416g, 3mol) was added to a mixture of 4-bromo-4'-hydroxybiphenyl (300g, 1.2mol), 1-iodopentane

- 43 -

(234mL, 1.79mol) and 2-butanone (600mL). The reaction mixture was refluxed for 44h until TLC (85:15 hexanes/EtOAc) showed complete consumption of the bromo alcohol. The mixture was cooled to about 30°C, diluted with 5 CH₂Cl₂ (600mL) and then filtered. The filtrate was washed twice with H₂O and twice with a saturated aqueous NaCl solution, dried over anhydrous Na₂SO₄, filtered and then dried at reduced pressure to provide a solid. This solid was isolated by filtration, washed repeatedly with a total 10 of 2L of ice-cold heptane to remove all traces of iodopentane and then dried overnight under high vacuum. Yield: 340g (88%) of a white powder.

Alternative Preparation of 4-bromo-4'-pentyloxybiphenyl

15 4-Bromo-4'-hydroxybiphenyl (12.5g, 50.2mmol) was added to a solution of NaOH (2.28g, 97% pure, 55.2mmol) in deionized H₂O (150mL), followed by the addition of 1-iodopentane (11.9g, 60.2mmol) and tetrabutylammonium bromide (0.82g, 2.51mmol). The mixture was stirred at 90°C 20 for 3.75h until the solids went into solution. Then, as the reaction proceeded, the desired product began to precipitate. The mixture was slowly cooled and then filtered to provide a solid which was washed with deionized water until the pH of the filtrate was neutral and then 25 dried for 16h in a vacuum oven at 30°C.

Yield: 15.41g (96%) of 5a. R_f 0.5 (97:3 hexanes/EtOAc).

¹H NMR: δ 0.93 (t, 3H, J=6.9Hz); 1.41 (m, 4H); 1.79 (m, 2H); 3.97 (t, 2H, J= 6.6Hz); 6.98 (m, 2H); 7.23 (m, 6H).

30 ¹³C NMR: δ 14.03; 22.43; 28.22; 28.98; 68.12; 114.91; 120.71; 127.93; 128.27; 131.77; 132.24; 139.82; 159.03.

MS(FAB⁺): m/z 320.

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IR(CHCl₃): 2960, 2936, 2974, 1608, 1516, 1485, 1475 cm⁻¹.

Analysis for C₁₇H₁₉BrO:

Calcd: C, 63.96; H, 6.00; Br, 25.0;

Found: C, 64.10; H, 5.97; Br, 25.28.

5

B. 4-Boronic acid-4'-pentyloxybiphenyl

To a cold (-20°C) mixture of Preparation 8A (100g, 0.31mol) in MTBE (1L), was slowly added n-butyl lithium (150mL of a 2.5M hexanes solution, 0.37mol) dropwise under N₂, while maintaining the internal temperature between -19° and -18°C. The resultant mixture was stirred for 3.5h between -17° and -16°C which resulted in light yellow-green solution. This solution was cooled to -78°C and diluted with 100mL of anhydrous THF which resulted in a white precipitate. Then, a cold (-78°C) solution of triisopropylborate (145mL, 0.62mol) in MTBE (200mL), under nitrogen was added dropwise over 1.5h while maintaining the reaction temperature between -78° and -74°C. The resultant reaction mixture was stirred for 1.5h at -78°C, then allowed to warm to -50°C over 1h at which time the cooling bath was removed and the mixture was stirred overnight (16-21h) which resulted in a white precipitate. The mixture was shaken vigorously with 2M HCl (1000mL) for 5 minutes and then the resulting layers were separated and the organic layer was dried at reduced pressure to provide a residue. This residue was diluted with MTBE (100mL), followed by heptane (800mL) to provide a white powder which isolated by suction filtration and washed 3 times with heptane (300mL).

Yield: 88g (98%).

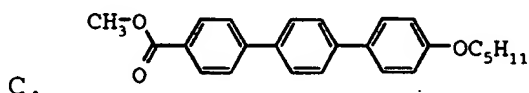
R_f 0.45 (95:5 CH₂Cl₂/MeOH).

¹H NMR: δ 0.92 (m, 3H); 1.41 (m, 4H); 1.80 (m, 2H); 4.00 (m, 2H); 6.99 (m, 2H); 7.45-7.63 (m, 3H); 7.67 (m,

- 45 -

2H); 8.24 (d, 1H, J=8.3Hz).

¹³C NMR: 14.01; 22.26; 28.03; 28.77; 39.61; 39.89; 40.17;
40.45; 67.82; 114.77; 125.32; 127.83; 132.93; 134.84;
141.88; 158.71.

5 MS(FD⁺): m/z 284.IR(CHCl₃): 2959, 2952, 2874, 1606, 1526, 1500 cm⁻¹.

10 A solution of toluene (174mL) and propanol (20mL) was
degassed 3 times by applying vacuum to the solution for 20-
30 seconds followed by purging with N₂. A 2M solution of
Na₂CO₃ was also degassed. The toluene/propanol solution
(97mL) was added to a mixture of methyl 4-iodobenzoate
(14.12g, 53.9mmol) and Preparation 8B (15.0g, 52.8mmol),
15 followed by a degassed 2M aqueous Na₂CO₃ solution (29mL,
58.0mmol). The resultant mixture was degassed 2 times for
20-30 seconds each under a positive pressure of N₂, followed
by the addition of palladium (II) acetate (0.24g, 1.1mmol)
and triphenylphosphine (0.84g, 3.2mmol) and then degassed 2
20 more times. The reaction mixture was then refluxed under N₂
for 5h resulting in a light-yellow mixture. This mixture
was cooled to 23°C resulting in the formation of a
precipitate which was collected by filtration, washed
successively with toluene (123mL), 2:1 MTBE/EtOAc (143mL),
25 deionized water (123mL) and 2:1 MTBE/EtOAc (42mL) and then
dried for 16h in a vacuum oven at 35°C.

Yield: 18.7g (94%).

R_f 0.48 (benzene).

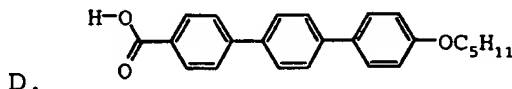
30 ¹H NMR: δ 0.93 (t, 3H, J=6.80Hz); 1.42 (m, 4H); 1.81 (m,
2H); 3.95 (s, 3H); 4.00 (t, 2H, J= 6.48 Hz); 6.97 (d,
2H, J=8.52Hz); 7.55 (d, 2H, J= 8.52Hz); 7.66 (m, 6H),
8.10 (d, 2H, J=8.20Hz).

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MS(FD⁺): m/z 374.IR(KBr): 2938, 1723 cm⁻¹.Analysis for C₂₅H₂₆O₃:

Calcd: C, 80.18; H, 7.00;

5 Found: C, 79.91; H, 6.94.



A mixture of Preparation 8C (80g, 0.21mol), 5M KOH (160mL) and cetyltrimethylammonium bromide (4.8g, 0.013mol)
10 in xylene (800mL) was refluxed for 3h and then cooled to 10°C and filtered to provide a white solid. This solid was washed 3 times with H₂O (500mL each) to remove the catalyst and most of the base. The resultant material was treated with DME (500 ml). The pH of the solution was adjusted to
15 pH by the addition of 6M HCl (100mL). The resultant mixture was refluxed for 30 minutes while periodically checking the pH to assure that it remained acidic, then cooled and filtered. The resulting solid was washed successively with MTBE (400mL) and water (4x400mL) until
20 the washings were neutral to litmus.
Yield: 76 g (98% yield).

¹H NMR δ 0.89 (t, 3H, J= 6.82Hz), 1.38 (m, 4H), 1.73 (m, 2H), 3.96 (t, 2H, J= 6.3Hz), 6.95 (d, 2H, J=8.56Hz),
7.57 (d, 2H, J=8.54Hz), 7.64-7.74 (m, 6H), 8.00 (d, 2H, J=8.21Hz), 8.09 (s, 1H).
25

MS(FD⁺) m/z 360.IR(KBr): 2958, 2937, 2872, 1688 cm⁻¹.Analysis for C₂₄H₂₄O₃:

Calcd: C, 79.97; H, 6.71;

30 Found: C, 80.50; H, 6.77.

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E. HOBT ester of Preparation 8D

1. Formation of HOBT mesylate

To a cold (0°C) mixture of hydroxybenzotriazole hydrate (200g, 1.48mol) in anhydrous CH₂Cl₂ (1.5L), was slowly added
5 anhydrous Et₃N (268mL, 1.92mol) while maintaining a

temperature of 0-10°C, followed by the addition of methanesulfonyl chloride (126mL, 1.63mol) while maintaining a temperature of 0-5°C. The resultant mixture was stirred for 3h at 0°C and washed successively with cold water (2 x
10 1.2L) and brine (1.2L). The combined organic extracts were concentrated at reduced pressure to provide a solid. This solid was recrystallized from CH₂Cl₂ (100mL) and heptane (1L). The crystals were collected by suction filtration and washed repeatedly with a total of 1.L of heptane and
15 then dried overnight under high vacuum (0.5 mm Hg).

Yield: 245g (78%)

R_f 0.55 (1:1 hexanes/CH₂Cl₂).

¹H NMR: δ 3.58 (s, 3H), 7.46 (t, 1H, J= 7.60Hz), 7.60
(d, 1H, J= 8.28 Hz), 7.65 (d, 1H, J= 8.56Hz), 7.68 (d,
20 1H, J= 8.20 Hz), 8.05 (d, 1H, J=8.41Hz).

2. Formation of HOBT ester

A mixture of Preparation 8D (50g, 0.14mol) and Preparation 8E-1 (36g, 0.17mol) in DMF (650mL) was treated dropwise with Et₃N (25mL, 0.18mol), under N₂. The resultant
25 mixture was stirred for 4h at room temperature until all the acid was consumed, as determined by TLC (95:5 CH₂Cl₂/MeOH).

When all the acid was consumed, an aliquot of the reaction mixture (~ 3 pipet drops) gave a clear homogeneous solution
30 when diluted with 3mL of 1:1 CH₂Cl₂/THF. The reaction mixture was then diluted with toluene (500mL), washed with water (500mL). The organic layer (containing solid product) was diluted with water (500mL) and filtered using

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MTBE for transferring. The solid was rinsed with MTBE (2 x 400mL) and dried under vacuum to provide green-white flakes of material. NOTE: This material could be dissolved in THF and filtered to remove any remaining metal contamination.

Yield: 61g (92%).

R_f 0.68 (1:1 CH₂Cl₂/hexanes).

¹H NMR: δ 0.93 (t, 3H, J=7.0Hz), 1.42 (m, 4H),, 1.81 (m, 2H), 4.00 (t, 2H, J=6.53Hz), 6.99 (d, 2H, J=8.6Hz), 7.42-7.59 (m, 5H), 7.71 (dd, 4H, J=13.91Hz, 8.40Hz), 7.86 (d, 2H, J=8.30Hz), 8.11 (d, 1H, J= 8.31Hz), 8.35 (d, 2H, J=8.33Hz).

¹³C NMR: δ 14.03, 22.44, 28.18, 28.94, 40.10, 40.37, 68.11, 108.45, 110.11, 114.95, 118.71, 120.48, 123.04, 124.94, 124.99, 127.00, 127.23, 127.51, 127.73, 128.06, 128.82, 128.86, 131.35, 132.30, 137.15, 141.43, 143.54, 147.85, 159.15, 162.73.

MS(FD⁺): m/z 477.

IR(CHCl₃): 2960, 2936, 2874, 1783, 1606 cm⁻¹.

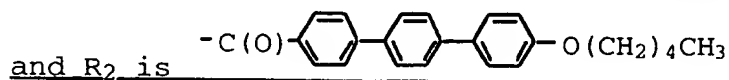
Analysis for C₃₀H₂₇N₃O₃:

Calcd: C, 75.45; H, 5.70; N, 8.80;

Found: C, 75.69; H, 5.58; N, 8.92.

Preparation 9

A. Cyclic peptide of formula IIB where R', R'', and R''' are each methyl, R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} are each hydroxy



NOTE: Deionized water was used throughout this operation. A mixture of Preparation 8E (11g, 23mmol) and the cyclic peptide of formula IIB where R', R'', and R''' are methyl, R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, R^{y4} are each hydroxy and R₂ is hydrogen (92% pure by HPLC, 19.25 g, 22.2mmol) in anhydrous DMF (275mL) was stirred, under N₂ for 4h (until

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HPLC showed complete consumption of the cyclic peptide starting material). The mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure at 35°C to provide a paste that could be stirred.

5 This paste was poured into MTBE (500mL) which resulted in the precipitation of a fine powder which was collected by vacuum filtration and dried to provide 27g of crude material. This material was crushed to a powder with a mortar and pestle, slurried for 5 minutes in toluene
10 (200mL), suction filtered (slow filtered), rinsed with MTBE (100mL) and then dried in vacuo to provide a yellow solid. Yield: 23 g (95% pure by HPLC, retention time = 7.79 min).

Alternatively, Preparation 9A may be carried out
15 using an excess of the cyclic nucleus (1.1 equiv.). When the reaction was substantially complete, as indicated by HPLC, the crude material (10g of a powder) was added portion-wise to a vigorously stirred mixture of 9:1 acetone/water (60mL). Celite (2.5 g, pre-washed with a 9:1
20 acetone/water mixture) was added to the resultant suspension. After stirring for 2 minutes, the mixture was filtered through a bed of celite (prewashed with 9:1 acetone/water) and the cake was rinsed twice with 9:1 acetone/water (10mL). The filtrate was poured into a
25 beaker of deionized water (200mL) while gently swirling the mixture which resulted in the formation of a precipitate. This precipitate was collected by suction filtration, rinsed with H₂O (4 x 25mL), and then dried in vacuo at room temperature.

30 Yield: 6.81g (97% pure by HPLC).

The product was further purified using preparatory HPLC chromatography.

R_f 0.29 (80:20 CHCl₃/MeOH).

HRMS(FAB⁺): m/z for C₅₈H₇₄N₇O₇

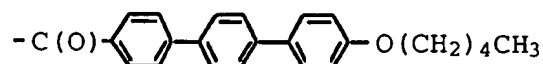
- 50 -

Calcd: 1140.5141;

Found: 1140.5103.

IR(KBr): 3365, 2934, 1632, 1518 cm^{-1} .

5 B. Cyclic peptide of formula I where R' , R'' , and R''' are
each methyl, R^{x1} and R^{x2} are each hydrogen, R^{y1} , R^{y2} , R^{y3} ,
 R^{y4} are each hydroxy and R_2 is



10 To a cool (16°C) solution containing Preparation 9A
 (0.235 kg, 0.207mol, 1.0 equiv.) and triethylsilane
 (0.78kg, 6.70mol, 30 equiv.) in CH_2Cl_2 (0.77L), was slowly
 added CF_3COOH (0.978 kg, 8.56mol, 35 equiv.) while
 maintaining the temperature at 20°C. After 90 minutes, the
 mixture was cooled to -5°C, diluted with THF (4.0L) and
 15 poured into a solution of K_2CO_3 (0.862 kg, 8.62mol, 38.5
 equiv.) in H_2O (4.0L). The resulting layers were separated
 and the organic layer was dried in vacuo to provide 0.308
 kg of crude material (yield: 83.1% after correction for
 potency (61.7%)). The crude material was purified using
 20 HPLC (HP20SS column by step gradient elution; solvent A -
 42:58 MeCN/0.1% HOAc at pH 5; solvent B - 60:40 MeCN/0.1%
 HOAc at pH 5).

IR (CHCl_3): 3366, 2934, 1636, 1517 cm^{-1} .HRMS (FAB⁺): m/z for $\text{C}_{58}\text{H}_{74}\text{N}_7\text{O}_{15}$:

25 Calcd: 1108.5243;

Found: 1108.5265.

Analysis for $\text{C}_{58}\text{H}_{73}\text{N}_7\text{O}_{15}$:

Calcd: C, 62.85; H, 6.63; N, 8.85;

Found: C, 62.90; H, 6.49; N, 8.96.

30

Preparation 10A. Methyl-6-O-t-butyldimethylsilyl- α -D-mannopyranoside

The C-6 hydroxy of methyl- α -D-mannopyranoside (7.20g,
 37.1mmol) was protected as the t-butyldimethylsilyl ether

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using imidazole (5.05g, 74.2mmol) and t-butyldimethylsilyl chloride (6.15g, 40.8mmol) in DMF (50mL). The crude product was purified using silica gel chromatography (2:1 EtOAc:hexanes).

5 Yield: 7.00 g (61%) of a white solid.

B. Methyl-6-O-t-butyldimethylsilyl-2,3-O-isopropylidene- α -D-mannopyranoside

To a solution containing Preparation 10A (3.3g, 10.72mmol) and pyridinium p-toluenesulfonate (2g, 7.5mmol) in acetone (20mL), was added 2,2-dimethoxypropane (13.2mL, 107.2mmol). The reaction mixture was stirred for 1h at room temperature. When the reaction was substantially complete, as indicated by TLC, the reaction was quenched by the addition of a saturated aqueous sodium bicarbonate solution (NaHCO₃) (30mL) and then diluted with EtOAc. The resulting layers were separated and the aqueous layer was extracted with EtOAc (2 x 30mL). The combined organic extracts were washed with brine (50mL), dried over Na₂SO₄, filtered and then concentrated in vacuo to provide a viscous yellow oil. This oil was purified using silica gel chromatography (1:1 hexanes/Et₂O).

Yield: 3.4 g (91%) of a clear viscous oil.

IR (CHCl₃): 3590 cm⁻¹ (OH).

25 ¹H NMR (DMSO-d₆): δ 0.02 (s, 6H), 0.84 (s, 9H), 1.22 (s, 3H), 1.36 (s, 3H), 3.28 (s, 3H), 3.28-3.32 (m, 1H), 3.56-3.62 (dd, 1H, J=3, 1Hz), 3.80-3.92 (m, 2H), 3.96 (d, 1H, J=3Hz), 4.78 (s, 1H), 5.16 (d, 1H, J=3 Hz);.

30 ¹³C NMR (DMSO-d₆): δ 18.35, 26.15, 26.66, 28.36, 54.12, 59.57, 62.92, 68.28, 71.36, 75.51, 79.07, 97.58, 108.61.

MS (FD+): m/z 349.

Analysis for C₁₆H₃₂O₆Si:

35 Calcd: C, 55.14; H, 9.25;

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Found: C, 54.91; H, 9.14.

Preparation 11

Methyl-6-O-t-butyldiphenylsilyl-2,3-O-isopropylidene- α -D-mannopyranoside

5

In a similar manner to Preparation 10, the C-6 hydroxy of methyl- α -D-mannopyranoside was protected as the t-butyldiphenylsilyl ether, followed by formation of the dimethyl acetal to provide a clear oil.

10 IR (CHCl₃): 3595 cm⁻¹ (OH).

¹H NMR (DMSO-d₆): δ 1.02 (s, 9H), 1.28 (s, 3H), 1.42 (s, 3H), 3.38 (s, 3H), 3.38-3.44 (m, 1H), 3.48-3.54 (m, 1H), 3.72-3.80 (dd, 1H, J=3, 1Hz), 3.92-4.00 (m, 2H), 4.06-4.12 (d, 1H, J=3Hz), 4.92 (s, 1H), 5.22 (d, 15 1H, J=3Hz), 7.36-7.50 (m, 6H), 7.66-7.80 (m, 4H).

¹³C NMR (DMSO-d₆): δ 19.6, 27.31, 28.72, 54.57, 64.17, 68.64, 71.67, 75.91, 79.37, 98.07, 109.04, 128.59, 130.56, 133.94, 135.78, 136.03.

MS (FD+): m/z 473.

20 Analysis for C₂₆H₃₆O₆Si:

Calcd: C, 66.07; H, 7.68;

Found: C, 65.98; H, 7.50.

Preparation 12

25

A. Methyl-4,6-O-benzylidene- α -D-glucopyranoside

To a mixture of methyl- α -D-glucopyranoside (10.05g, 51.2mmol) and camphor sulfonic acid (0.985g, 4.24mmol) in CH₃CN (70mL), was slowly added benzaldehyde dimethylacetal (9.28mL, 61.0mmol). The resulting mixture was reacted 30 overnight at reflux temperature, under N₂. When the reaction was substantially complete, as indicated by TLC (90:10 CH₂Cl₂/MeOH), an excess of Et₃N (10mL, 71mmol) was added and the resulting mixture was concentrated in vacuo to provide a tan solid. This solid was recrystallized from 35 warm propanol/pyridine (28mL/0.5mL), collected by vacuum

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filtration, rinsed with 1:1 MTBE/hexanes (50mL) and then dried in vacuo.

Yield: 9.08 g (62%) of a yellow-white solid.

IR (CHCl₃): 3595 cm⁻¹ (OH).

5 ¹H NMR (DMSO-d₆): δ 3.36 (s, 3H), ~~3.36-3.42 (m, 1H)~~,
3.54-3.62 (m, 1H), 3.64-3.74 (t, 1H, J=6 Hz), 4.16-
4.22 (dd, 1H, J=3, 1 Hz), 4.64 (d, 1H, J=2 Hz), 5.00
(d, 1H, J=3 Hz), 5.18 (d, 1H, J=3 Hz), 5.58 (s, 1H),
7.36-7.52 (m, 5H).

10 ¹³C NMR (DMSO-d₆): δ 26.62, 55.75, 63.38, 69.18, 70.89,
73.42, 82.35, 101.55, 101.86, 127.39, 129.01, 129.83,
138.83.

MS (FD+): m/z 282.

15 B. Methyl-2,3-di-O-acetyl-4,6-O-benzylidene- α -D-
glucopyranoside

Acetic anhydride (2.1mL, 22.16mmol) was slowly added
to a solution of Preparation 12A (2.844g, 10.07mmol), Et₃N
(3.5mL, 25.2mmol) and a catalytic amount of 4-
20 dimethylaminopyridine (DMAP) (0.10 g) in CH₂Cl₂ (25mL).
When the reaction was substantially complete, as indicated
by TLC (1:1 hexanes/EtOAc), the mixture was diluted with
CH₂Cl₂ (25mL) and aqueous NaHCO₃ (25mL). The resulting
layers were separated and the aqueous layer extracted with
25 CH₂Cl₂ (2 x 30mL). The combined organic extracts were
washed with brine (50mL), dried over Na₂SO₄, filtered and
then concentrated in vacuo to provide a clear viscous oil
which solidified on standing. This material was used
without further purification.

30 Yield: 3.35 g (91%).

¹H NMR (CDCl₃): δ 2.02 (s, 3H), 2.06 (s, 3H), 3.46 (s, 3H),
3.62-3.66 (t, 1H, J=4.5 Hz), 3.70-3.76 (t, 1H,
J=4.5 Hz), 3.92-3.98 (m, 1H), 4.36 (q, 1H, J=2 Hz),
4.98 (m, 2H), 5.50 (s, 1H), 5.58 (t, 1H, J=3 Hz),
35 7.32-7.50 (m, 5H).

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C. Methyl-2,3-di-O-acetyl-6-O-benzyl-
 α -D-glucopyranoside

To a cold (0°C) solution of Preparation 12B (3.35g, 9.14mmol) in CH₂Cl₂ (25mL), was slowly added ~~CF₃COOH~~ (3.52mL, 45.7mmol). After stirring for 5 minutes, triethylsilane (7.30mL, 45.7mmol) was slowly added. The reaction mixture was then allowed to warm to room temperature. When the reaction was substantially complete, as indicated by TLC (1:1 hexanes/EtOAc), the mixture was diluted with EtOAc (50mL) and aqueous NaHCO₃ (60mL). The resulting layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 x 50mL). The combined organic extracts were washed with brine (60mL), dried over Na₂SO₄, filtered and then concentrated in vacuo to provide a yellow oil. The oil was purified using silica gel chromatography to provide a clear viscous oil.

Yield: 3.052 g (91%).

IR (CHCl₃): 3490 (OH), 1745 cm⁻¹ (C=O).

¹H NMR (DMSO-d₆): δ 1.98 (s, 3H), 2.02 (s, 3H), 3.34 (s, 3H), 3.40-3.56 (m, 1H), 3.58-3.76 (m, 2H), 4.56 (s, 2H), 4.62-4.70 (dd, 1H, J=3,1 Hz), 4.82 (d, 1H, J=1.5Hz), 5.12-5.22 (dd, 1H, J=6, 1Hz), 5.56 (d, 1H, J=3Hz), 7.24-7.42 (m, 5H).

¹³C NMR (DMSO-d₆): δ 20.61, 20.88, 54.61, 67.89, 69.08, 70.82, 71.16, 72.36, 72.49, 96.29, 127.48, 128.38, 138.62, 169.88, 169.99.

MS (FD+): m/z 368.

Preparation 13

A. Methyl-2,3,6-tri-O-benzyl-4,6-O-benzylidene- α -D-
glucopyranoside

A solution of Preparation 12A (1.88g, 6.66mmol) and tetrabutylammonium iodide (0.246g, 0.67mmol) in DMF (10mL) was slowly added to a cold (0°C) stirring mixture of sodium

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hydride (60% oil dispersion, washed with hexanes, 0.67g, 16.6mmol) in DMF (10mL). The resulting mixture was cooled to 0°C, followed by the dropwise addition of benzyl bromide (1.75mL, 14.6mmol). After stirring at 0°C for 10 minutes, the mixture was allowed to warm to room temperature. When the reaction was substantially complete, as indicated by TLC (1:1 hexanes/EtOAc), excess MeOH (20mL) was added which resulted in the evolution of gas. The resulting mixture was diluted with Et₂O (50mL) and aqueous NaHCO₃ (50mL). The resulting layers were separated and the aqueous layer was extracted with Et₂O (2 x 50mL). The combined organic extracts were washed with brine (50mL), dried over anhydrous Na₂SO₄, filtered and then concentrated in vacuo to provide a reddish brown oil which solidified on standing. This material was purified using silica gel chromatography (5:1 hexanes/EtOAc) to provide a white solid. Yield: 1.62 g (53%).

¹H NMR(DMSO-d₆): δ 3.34 (s, 3H), 3.56-3.84 (m, 5H), 4.18-4.24 (dd, 1H, J=4.5, 3Hz), 4.66 (s, 2H), 4.78 (s, 2H), 4.90 (d, 1H, J=1.5Hz), 5.66 (s, 1H), 7.20-7.50 (m, 15H).

¹³C NMR (DMSO-d₆): δ 54.62, 62.09, 67.97, 71.74, 73.59, 77.49, 79.03, 80.87, 97.92, 100.26, 125.93, 127.21, 127.39, 127.54, 127.97, 128.01, 128.12, 128.69, 137.59, 138.36, 138.76;

MS (FD+): m/z 462.

B. Methyl-2,3,6-tri-O-benzyl-α-D-glucopyranoside

To a solution of Preparation 13A (1.62g, 3.5mmol) in THF (5mL), was added 1M sodium cyanoborohydride in THF (36mL, 36mmol). A solution of Et₂O (10mL) saturated with HCl gas was added slowly and the reaction flask was vented through a drying tube (the reaction mixture was pH 3). When the reaction was substantially complete, as indicated by TLC (1:1 hexanes/EtOAc), the mixture was diluted with

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Et₂O (50mL) and aqueous NaHCO₃ (75mL). The resulting layers were separated and the aqueous layer was extracted with Et₂O (2 x 30mL). The combined organic extracts were dried over Na₂SO₄, filtered and then concentrated in vacuo to provide a viscous greenish-yellow oil. This oil was

purified using silica gel chromatography (1:1 hexanes/EtOAc) to provide a colorless viscous oil. Yield: 1.25 g (77%).

¹H NMR (CDCl₃): δ 2.94 (br.s, 1H), 3.38 (s, 3H), 3.50-3.90 (m, 6H), 4.48-4.82 (m, 6H), 5.06 (d, 1H, J=3Hz), 7.10-7.44 (m, 15H).

MS (FD+): m/z for C₂₈H₃₂O₆:

Calcd: 464.5;

Found: 463.1 (M-H).

Analysis for C₂₈H₃₂O₆:

Calcd: C, 72.39; H, 6.94;

Found: C, 72.02; H, 6.99.

Example 1

4-Bromobenzyl methylphosphonate derivative of Preparation

9B

A solution of Preparation 9B (91% pure by HPLC, 5.3g, 4.35mmol) in DMF (13mL) was added dropwise to a solution of lithium t-butoxide (t-BuOLi) (95% pure, 0.43g, 5.13mmol) in DMF (13mL). The reaction mixture was stirred at room temperature until a dark brown solution formed. After cooling to 0°C, a solution of Preparation 6A (97.7% pure, 2.69g, 5.13mmol) in THF (26mL) was added dropwise (0.4mL/min). When the reaction was substantially complete, as indicated by HPLC (1-2% of Preparation 9B remained), the reaction was quenched by the addition of acetic acid (2 equiv. relative to the amount of base used). After 15 minutes, the mixture was poured into CH₃CN, resulting in the formation of a precipitate which was collected by filtration, dried in vacuo and redissolved in MeOH (10.5mL). The resulting solution was poured into H₂O

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(133mL) resulting in the formation of a precipitate and the mixture was stirred vigorously for 10 minutes and then filtered to provide 4.6 g (84% yield, corrected for 87.7% potency). This material was purified using silica gel chromatography (85:15 CH₂Cl₂/MeOH). R_f 0.43 (90:10

CH₂Cl₂/MeOH).

IR(CHCl₃): 3338, 2937, 2876, 1639, 1609, 1529 cm⁻¹.

MS(FAB+) m/z 1356.

10 The reaction described in Example 1 was conducted with different combinations of solvents, base and amounts of reactants with the following results.

Base (mol eq.)	Compound of Prep.6A (mol eq.)	Solvent	% Compound of Prep. 9B remaining	% Compound of Ex. 1	% By- products
LiOH (2.2)	1.5	DMF	15	74	3.0
LiOH (1.0)	2.0	2:3 DMF/THF	23	74	0.1
LiOH(1.05)	2.0	DMF	<1	95	1.5
LiOH (2.2)	2.0	DMF	<1	80	16.0
LiOTMS (1.1)	1.1	1:1 DMF/THF	5	89	1.5
LiOTMS (1.3)	1.2	1:1 DMF/THF	3	90	1.7
t-BuOLi (1.0)	1.1	2:3 DMF/THF	5	86	1.8
t-BuOLi (1.18)	1.18	1:1 DMF/THF	<1	94	1.0
t-BuOLi (1.25)	1.33	1:1 DMF/THF	<1	94	1.5

15 Reactions were run with 0.5-2.0 g of Preparation 9B. A 3M aqueous solution of LiOH was used. The percent (%) of Preparation 9B remaining was calculated using UV area percent by HPLC. The % by-products corresponds to the percent of late-eluting by-products by HPLC.

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Example 24-Bromobenzyl methylphosphonate derivative of
Preparation 9B

To 0.45 g (0.88mmol) of one diastereomer of di-(4-bromobenzyl) dimethylpyrophosphonate prepared using the recrystallization described in Preparation 6B, was added 0.65 g (0.60mmol) of Preparation 9B and 3mL of DMF. The solution was cooled to -10°C and 0.32mL (0.64mmol) of 2M aqueous LiOH was added over 1.5h. The mixture was allowed to warm to 0°C and an additional 0.12mL of 2M LiOH was added. Acetic acid was added until the pH was 7 and the mixture was poured into 100mL of CH₃CN. The resulting solid was collected by filtration, rinsed with methyl t-butyl ether and dried in vacuo to provide 0.83 g of the titled compound.

Example 3Phosphonic Acid derivative of Preparation 9B

Example 1 (97% pure, 100 mg, 0.08mmol) was hydrogenated using 10% Pd/C (50 mg), Et₃N (0.03mL, 0.22mmol) in 90:10 THF/DMF (1.5mL), under 1 atm of H₂. After 3h, the mixture was filtered through celite and rinsed with THF (10mL). The filtrate was concentrated in vacuo to provide a residue which was triturated with MeCN (10mL) and then filtered to provide a white solid. This solid was rinsed with Et₂O (2 x 3mL) to provide 65 mg (74%) of crude material which was purified using HPLC chromatography.

IR (KBr): 3369, 2933, 1634, 1507, 1436 cm⁻¹.

HRMS (FAB⁺) m/z for C₅₈H₇₇N₇O₁₇P:

Calcd: 1186.5114.

Found: 1186.5139.

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Example 4Benzyl methylphosphonate derivative of Preparation 9B

A solution of 2.4 g (2.17mmol) of Preparation 9B in 8mL of DMF was added to 1.54 g (4.35mmol) of Preparation 7 and rinsed with 2mL of DMF. The mixture was cooled to -10°C and 1.4mL (4.2mmol) of 3M aqueous LiOH was added over 1h. After an additional 30 minutes, 8.5mmol of acetic acid was added and the reaction mixture was poured into 150mL of cold CH₃CN. The resultant slurry was filtered and the solid was dried in vacuo to provide 1.9 g of material which was 87 area % of the phosphonate by HPLC. Purification of this material on silica gel using 14% MeOH and 1% acetic acid in CH₂Cl₂ provided the titled compound which was 94 area % by HPLC.

Example 5Phosphonic Acid Derivative of Preparation 9B

To a solution of 0.36 g of silica gel purified phosphonate from Example 4 in 2mL of THF and 0.5mL of H₂O was added 0.06 g of 10% Pd/C in 1mL of THF. After stirring for 2.5h under H₂, the mixture was filtered. The filtrate was concentrated to provide 0.27 g (83%) of a solid. HPLC analysis showed that the product was the same as that isolated in Example 3 with a purity of 92 area %.

Example 64-Bromobenzyl methylphosphonate derivative of diacetone-D-glucose

Diacetone-D-glucose (3.48g, 1.31mmol, 98% pure) in THF (15mL) was slowly added to a solution of t-BuOLi (1.325g, 1.57mmol, 95% pure) in THF (20mL) at 0°C. After 10 minutes, a solution of Preparation 6A (8.239g, 1.57mmol) in THF (75mL) was added slowly while maintaining a temperature of 0-5°C. The resulting mixture was allowed to warm to room temperature and stirred for 20h. When the reaction was substantially complete, as indicated by HPLC (consumption of the alcohol), the mixture was diluted with

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Et₂O (50mL) and aqueous NaHCO₃ (50mL). The resulting layers were separated and the aqueous layer was extracted with Et₂O (2 X 50mL). The combined organic layers were washed with brine (100mL), dried over Na₂SO₄, filtered and then concentrated in vacuo to provide a viscous yellow oil.

This oil was determined to be a mixture of diastereomers and was purified using silica gel chromatography (75:25 EtOAc/hexanes).

Yield: 5.62 g (85%) of a white solid.

IR (CHCl₃): 2995, 1250 cm⁻¹.

¹H NMR (DMSO-d₆): δ 1.18 (s, 3H), 1.24 (s, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.58-1.66 (d, 3H, J=10 Hz), 3.78-3.82 (m, 1H), 3.96-4.06 (m, 2H), 4.10-4.22 (m, 1H), 4.70-4.78 (m, 2H), 4.98-5.08 (m, 2H), 5.92 (d, 1H, J=3 Hz), 7.36-7.40 (d, 2H, J=6 Hz), 7.60-7.64 (d, 2H, J=6 Hz).

¹³C NMR (DMSO-d₆): δ 10.16, 12.03, 24.97, 25.93, 26.44, 65.37, 66.15, 71.62, 77.32, 79.76, 83.11, 104.44, 108.40, 111.32, 121.20, 129.54, 131.32, 136.00.

MS(FD+): m/z 506.9.

The following Examples 7-10 were prepared substantially in accordance with the procedure detailed in Example 6, using the designated starting material.

Example 7

4-Bromobenzyl methylphosphonate derivative of

Preparation 10B

IR (CHCl₃): 2932, 1251 cm⁻¹.

¹H NMR (CDCl₃): δ 0.10 (s, 6H), 0.84 (s, 9H), 1.26 (s, 3H), 1.44 (s, 3H), 1.58 (d, 3H, J=10Hz), 3.36 (s, 3H), 3.48 (q, 1H, J=3Hz), 3.64 (q, 1H, J=3Hz), 3.80 (d, 1H, J=6Hz), 4.12 (d, 2H, J=3 Hz), 4.20 (m, 2H), 4.90 (s, 1H), 4.92-5.08 (m, 2H), 7.18 (d, 2H, J=6Hz), 7.58 (d, 2H, J=6Hz);

- 61 -

^{13}C NMR (DMSO- d_6): δ 0.00, 10.53, 12.39, 17.81, 25.60,
26.15, 27.44, 53.99, 61.81, 64.73, 68.73, 72.99,
75.30, 76.55, 96.99, 109.10, 121.16, 129.44, 131.30,
136.02, 169.01.

5 MS (FD+): m/z 596.0.

Example 8

4-Bromobenzyl methylphosphonate derivative of Preparation

11

10 IR (CHCl₃): 2934, 1249 cm^{-1} .

^1H NMR (DMSO- d_6): δ 0.96 (s, 9H), 1.32 (s, 3H), 1.46 (s,
3H), 1.56-1.60 (d, 3H, $J=10\text{Hz}$), 3.38 (s, 3H), 3.64-
3.82 (m, 2H), 3.96 (d, 1H, $J=6\text{Hz}$), 4.06-4.14 (m, 2H),
4.24-4.40 (q, 1H, $J=4.5\text{ Hz}$), 4.58-4.68 (dd, 1H, $J=6$,
15 1.5Hz), 4.78-4.86 (dd, 1H, $J=6$, 1.5Hz), 5.04 (s, 1H),
7.12-7.20 (d, 2H, $J=6\text{Hz}$), 7.48 (m, 5 H), 7.58 (d, 2H,
 $J=6\text{ Hz}$), 7.60-7.72 (m, 5H).

^{13}C NMR (DMSO- d_6): δ 10.58, 12.44, 18.69, 26.15, 26.38,
27.45, 54.00, 59.29, 62.58, 64.50, 68.60, 73.09,
20 75.31, 76.46, 97.01, 109.14, 121.16, 127.67, 127.74,
129.48, 129.74, 131.22, 132.56, 132.82, 135.01,
168.99.

MS(FD+): m/z 720.

Analysis for C₃₄H₄₄O₈BrPSi:

25 Calcd: C, 56.74; H, 6.16;
Found: C, 56.53; H, 6.22.

Example 9

4-Bromobenzyl methylphosphonate derivative of Preparation 12C

30 ^1H NMR (CDCl₃): δ 1.40-1.44 (d, 3H, $J=10\text{ Hz}$), 1.84 (d, 6H,
 $J=3\text{ Hz}$), 3.60 (s, 3H), 3.86-3.96 (m, 1H), 4.24-4.58
(m, 4H), 4.82-5.16 (m, 5H), 5.34-5.42 (t, 1H,
 $J=6\text{Hz}$), 7.06-7.30 (m, 7H), 7.40-7.48 (m, 2H).

35 MS (FD+): m/z 615.

- 62 -

Analysis for $C_{26}H_{32}O_{10}BrP$:

Calcd: C, 50.74; H, 5.24;

Found: C, 50.74; H, 5.31.

5

Example 104-Bromobenzyl methylphosphonate derivative ofPreparation 13B

1H NMR (DMSO- d_6): δ 1.38-1.42 (d, 3H, $J=12$ Hz), 3.36 (s, 3H), 3.52-3.82 (m, 6H), 4.18-4.36 (m, 1H), 4.42 (d, 1H, $J=3$ Hz), 4.52 (d, 1H, $J=1.5$ Hz), 4.60-5.00 (m, 6H), 7.12 (d, 1H, $J=6$ Hz), 7.18-7.40 (m, 16H), 7.44 (d, 1H, $J=6$ Hz), 7.56 (d, 1H, $J=6$ Hz).

^{13}C NMR (DMSO- d_6): δ 10.96, 12.50, 54.86, 65.52, 68.77, 69.44, 71.61, 72.55, 73.86, 79.17, 79.39, 96.77, 121.20, 127.59, 127.66, 127.72, 127.78, 127.88, 128.19, 128.34, 129.61, 131.42, 131.56, 138.51, 138.74.

MS(FD+): m/z 711.5.

Example 11

20 4-Bromobenzyl methyl phosphonate derivative of (1R,2S,5R)-
(-)-menthol (Mixture of isomers)

To the alcohol (1 equiv.) in anhydrous THF (10-20mL/g of alcohol), was added t-BuOLi (1.1 eq.) in one portion. After cooling this mixture to 0°C, a solution of Preparation 6A (1.1 eq.) in THF/ (7-10 mL/g Preparation 6A) was slowly added dropwise. When the reaction was substantially complete, as indicated by TLC, excess 1N HCl was added and the resulting mixture was combined with EtOAc in a separatory funnel. The resulting layers were separated and the organic layer was washed sequentially with a 1:1 mixture of brine and aqueous $NaHCO_3$, brine, and then dried over Na_2SO_4 , filtered, and dried to provide crude material which was purified by silica gel chromatography.

IR ($CHCl_3$): 1490, 1222, 995 cm^{-1} .

35 1H NMR($CDCl_3$): δ 0.75 and 0.82 (d, 3H, $J=7$ Hz), 0.86

- 63 -

(m, 6H), 1.18 (m, 5H), 1.44 and 1.50 (d, 3H, J=3Hz), 1.66 (br.d, 2H, J=11 Hz), 2.07 and 2.21 (m, 2H), 4.21 (m, 1H), 5.00 (m, 2H), 7.25 (d, 2H, J=8 Hz), 7.49 (d, 2H, J=8Hz).

5 ^{13}C NMR (CDCl_3): δ 11.02, 12.03, 12.96, 13.96, 15.70, 20.93, 21.95, 22.85, 22.89, 25.56, 25.84, 31.50, 34.03, 43.11, 43.43, 48.39, 48.48, 65.81, 65.89, 66.02, 66.10, 122.31, 122.37, 129.44, 129.50, 131.37, 131.71, 135.63, 135.66, 135.71, 135.76.

10 MS(FD+): m/z 402 (^{79}Br), 404 (^{81}Br).

Analysis for $\text{C}_{18}\text{H}_{28}\text{O}_3\text{PBr}$:

Calcd: C, 53.61; H, 7.00;

Found: C, 53.84; H, 7.04.

15 The following Examples 12 and 13 were prepared substantially in accordance with the procedure detailed in Example 11.

Example 12

4-Bromobenzyl methyl phosphonate derivative of 4-methoxy-
20 phenol

IR(CHCl_3): 1505, 1200, 941 cm^{-1} .

^1H NMR(CDCl_3): δ 1.62 (d, 3H, J=17 Hz), 3.78 (s, 3), 5.05 (m, 2H), 6.82 (d, 2H, J=9 Hz), 7.07 (dd, 2H, J=1,10 Hz), 7.21 (d, 2H, J=8 Hz), 7.46 (d, 2H, J=8 Hz).

25 ^{13}C NMR (CDCl_3): δ 10.53, 12.45, 55.62, 66.85, 66.94, 114.72, 121.40, 121.45, 122.53, 129.67, 131.75, 135.07, 135.15, 143.69, 156.81.

MS(FD+): m/z 370 (^{79}Br), 372 (^{81}Br).

30 Example 13

4-Bromobenzyl methylphosphonate derivative of 1-phenyl-
ethanol (mixture of isomers)

IR (CHCl_3): 1490, 1312, 974 cm^{-1} .

^1H NMR (CDCl_3): δ 1.32 and 1.52 (d, 3H, J=17 Hz), 1.60

- 64 -

(dd, 3H, J=1, 6Hz), 4.54 and 4.78 (dd, 1H, J=8, 12Hz), 4.94 and 5.05 (dd, 1H, J=8 Hz, 12 Hz), 5.52 (m, 1H), 7.00 and 7.23 (d, 2H, J=8Hz), 7.36 (m, 6H), 7.50 (d, 1H, J=8Hz).

5 ¹³C NMR (CDCl₃): δ 11.12, 11.34, 13.02, 13.27, 24.47, 24.53, 24.63, 24.70, 65.71, 65.80, 65.83, 65.91, 74.75, 74.83, 75.13, 75.21, 122.17, 122.36, 125.90, 128.18, 128.24, 128.59, 128.63, 129.27, 129.50, 131.57, 131.72, 135.50, 141.77, 142.00.

10 Analysis for C₁₆H₁₈O₃PBr:

Calcd: C, 52.05; H, 4.91;

Found: C, 51.78; H, 4.84.

Example 14

15 Phosphonic acid derivative of Preparation 10B

Example 7 (0.48g, 0.80mmol) was hydrogenated using 10% Pd/C (50 mg), Et₃N (0.2mL, 1.6mmol) and 1 atm of H₂ in EtOAc (10mL). After 3h, the mixture was filtered through celite, rinsed with EtOAc (10mL) and then concentrated in vacuo.

20 Yield: 0.32 g (100% yield) of a viscous oil.

¹H NMR (CDCl₃): δ -0.06 (s, 6H), 0.74 (s, 9H), 1.18 (s, 3H), 1.24-1.28 (d, 3H, J=10 Hz), 1.44 (s, 3H), 3.22 (s, 3H), 3.24 (m, 1H), 3.52-3.60 (m, 1H), 3.88-4.20 (m, 3H), 4.80 (s, 1H), 5.66 (br, 1H).

25 MS (FD+): m/z 427.4.

Analysis for C₁₇H₃₈O₈PSi:

Calcd: C, 47.87; H, 8.27;

Found: C, 47.52; H, 8.98.

30 The following reaction was carried out in order to compare the present phosphorylation process with the phosphonic acid dichloride process known in the art.

Phosphonic Acid Derivative of Preparation 9B

35 A cold (0°C) solution of Preparation 9B (81% pure by UV, 2.3g, 1.68mmol) in anhydrous DMF (10mL), under N₂, was treated dropwise with a 1M LiOTMS in CH₂Cl₂ (2.5mL,

- 65 -

2.5mmol). The mixture was stirred for 10 minutes, followed by the dropwise addition of a solution of MeP(O)Cl₂ (1.1g, 8.2mmol) in anhydrous THF (2mL). The reaction was monitored by HPLC. After 10 minutes, HPLC showed 47%

5

~~starting material, 12% of the phosphonic acid, and other~~

by-product peaks. The reaction mixture was warmed to room temperature and stirred for 1h, followed by the addition of excess LiOTMS (2.5mL). The resulting mixture was stirred for 2h and then quenched by the addition of H₂O (3mL). The

10

reaction mixture was diluted with CH₃CN (80mL) which

resulted in the formation of a precipitate which was collected by filtration, washed with CH₃CN, and dried in

vacuo to provide 5 g of a white solid. HPLC analysis

indicated 37% starting material and 25% of the phosphonic

15

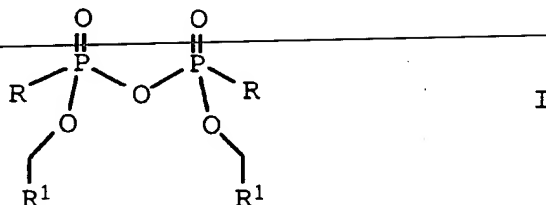
acid derivative of Preparation 9B. The desired compound was isolated by HPLC chromatography (HP20SS column by step gradient elution: solvent A - 42:58 MeCN/0.1% HOAc at pH 5; solvent B - 60:40 MeCN/0.1% HOAc at pH 5)..

20

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CLAIMS:

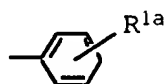
1. A compound of formula I:



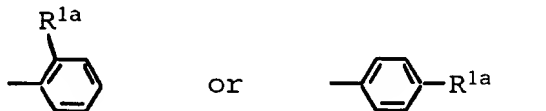
where:

R is C₁-C₆ alkyl, phenyl or benzyl;

R¹ is phenyl, naphthyl, cyclohexyl or a compound of the formula



where R^{1a} is hydrogen, halo, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl or benzyloxy; with the proviso that when R¹ is

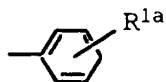


then R^{1a} cannot be hydroxy, C₁-C₆ alkoxy or benzyloxy; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 where:

R is C₁-C₄ alkyl;

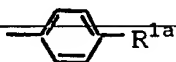
R¹ is phenyl or a compound of the formula



where R^{1a} is hydrogen, halo, C₁-C₆ alkyl or C₁-C₆ alkoxy; or a pharmaceutically acceptable salt thereof.

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3. A compound according to claim 2 where:
 R is methyl;
 R¹ is phenyl or a compound of the formula

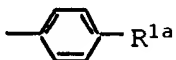


5

where R^{1a} is halo or hydrogen;
 or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 where:
 R¹ is phenyl or a compound of the formula

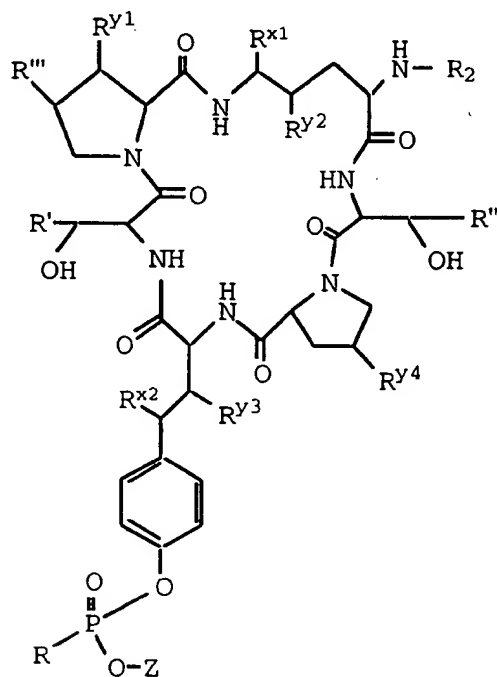
10



where R^{1a} is bromo or hydrogen;
 or a pharmaceutically acceptable salt thereof.

15

5. A compound of formula II



II

- 68 -

wherein:

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;

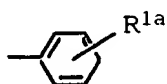
R" and R" are independently methyl or hydrogen;

R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, and R^{y4} are independently
 5 hydroxy or hydrogen;

R is C₁-C₆ alkyl, phenyl or benzyl;

Z is $-\text{CH}_2-\text{R}^1$;

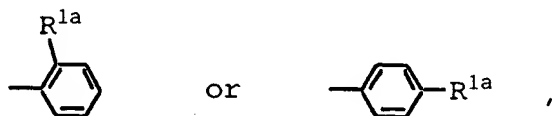
R¹ is phenyl, naphthyl, cyclohexyl or a compound of
 the formula



where R^{1a} is hydrogen, halo, trifluoromethyl, C₁-C₆ alkyl,
 C₁-C₆ alkoxy, hydroxy, cyano, nitro, protected amino,
 phenyl, benzyl or benzyloxy;

R₂ is acyl;

15 with the proviso that when R¹ is



then R^{1a} cannot be hydroxy, C₁-C₆ alkoxy or benzyloxy;
 or a pharmaceutically acceptable salt thereof.

20 6. A compound according to claim 5 where:

R', R" and R" are each methyl;

R^{x1} and R^{x2} are independently hydrogen or hydroxy;

R^{y1}, R^{y2}, R^{y3}, and R^{y4} are each hydroxy;

R is C₁-C₄ alkyl;

25 Z is $-\text{CH}_2-\text{R}^1$;

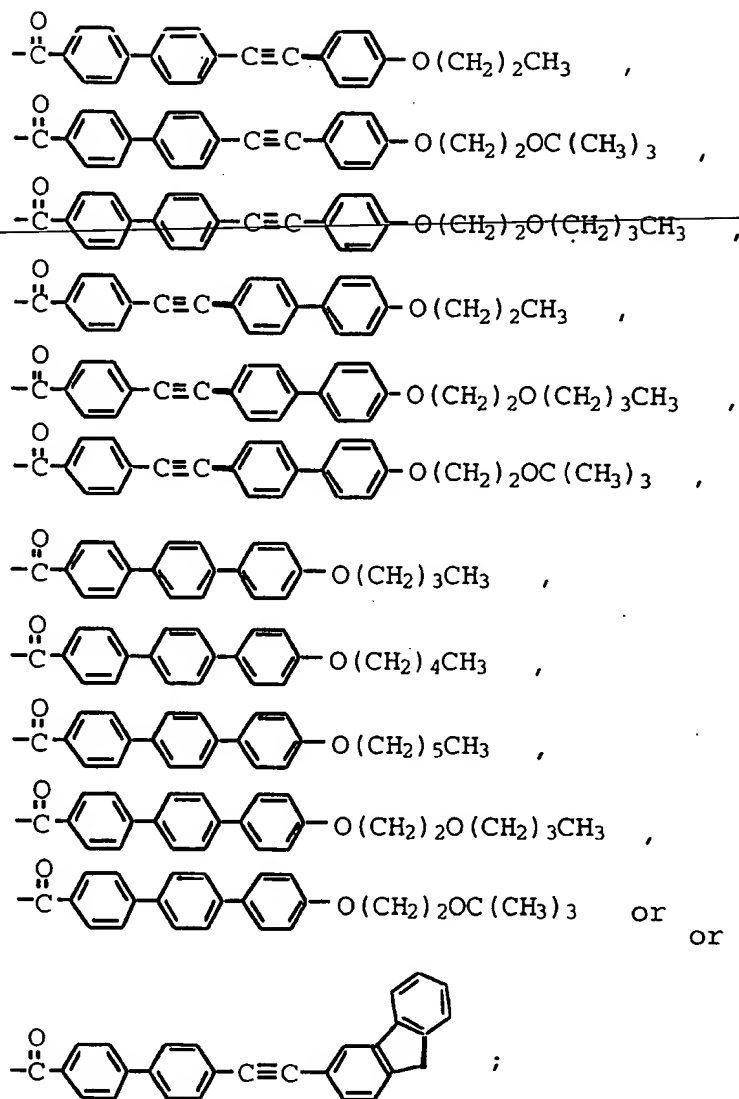
R¹ is phenyl, or a compound of the formula



where R^{1a} is hydrogen, halo, C₁-C₆ alkyl or C₁-C₆ alkoxy;

R₂ is an acyl group of the formula:

- 69 -



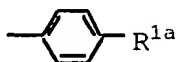
or a pharmaceutically acceptable salt thereof.

5

7. A compound according to claim 6 where:

R is methyl;

R¹ is phenyl or a compound of the formula



10

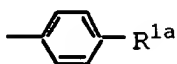
where R^{1a} is halo or hydrogen;

or a pharmaceutically acceptable salt thereof.

- 70 -

8. A compound according to claim 7 where:

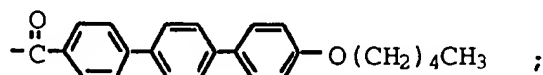
R^1 is phenyl or a compound of the formula



5 where R^{1a} is bromo or hydrogen;
or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8 where:

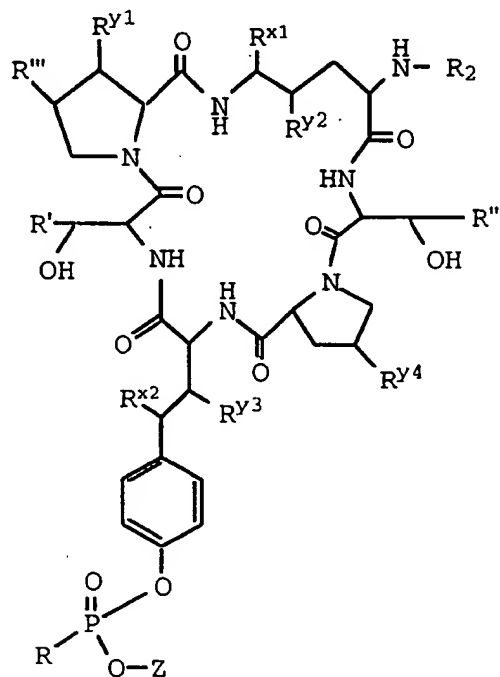
R_2 is



10

or a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound of formula IIA



IIA

15

wherein:

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;

R'' and R''' are independently methyl or hydrogen;

- 71 -

R^{x1} , R^{x2} , R^{y1} , R^{y2} , R^{y3} , and R^{y4} are independently hydroxy or hydrogen;

R is C₁-C₆ alkyl, phenyl or benzyl;

Z is hydrogen or -CH₂-R¹;

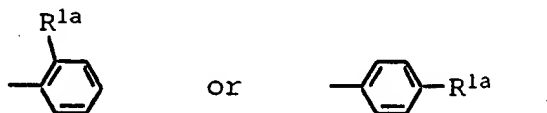
5 ~~R¹ is phenyl, naphthyl, cyclohexyl or a compound of~~
the formula



10 where R^{1a} is hydrogen, halo, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, cyano, nitro, protected amino, phenyl, benzyl, benzyloxy;

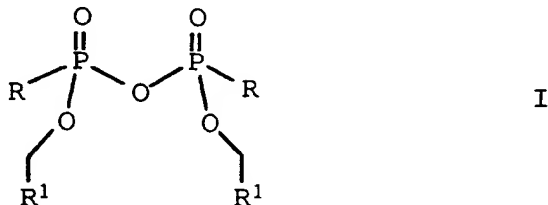
R₂ is an acyl side chain as defined herein;

with the proviso that when R¹ is



15 then R^{1a} cannot be hydroxy, C₁-C₆ alkoxy or benzyloxy; or a pharmaceutically acceptable salt thereof; which comprises

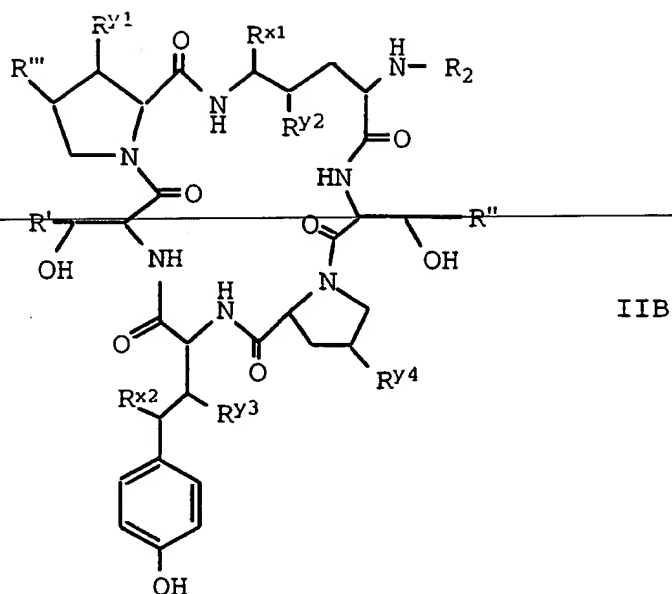
a) reacting a compound of formula I



20

with a compound of formula IIB

- 72 -



in the presence of a base at a temperature of from about
-30°C to about 40°C to provide a compound of formula II;

5 b) optionally converting the compound of formula II to
provide the compound of formula IIA where Z is hydrogen;
and

c) optionally forming a pharmaceutically acceptable
salt.

10

11. A process according to claim 10 for preparing a
compound of formula IIA where:

R', R'' and R''' are each methyl;

RX1 and RX2 are each hydrogen;

15 RY1, RY2, RY3, and RY4 are each hydroxy;

R is C₁-C₄ alkyl;

Z is -CH₂-R¹;

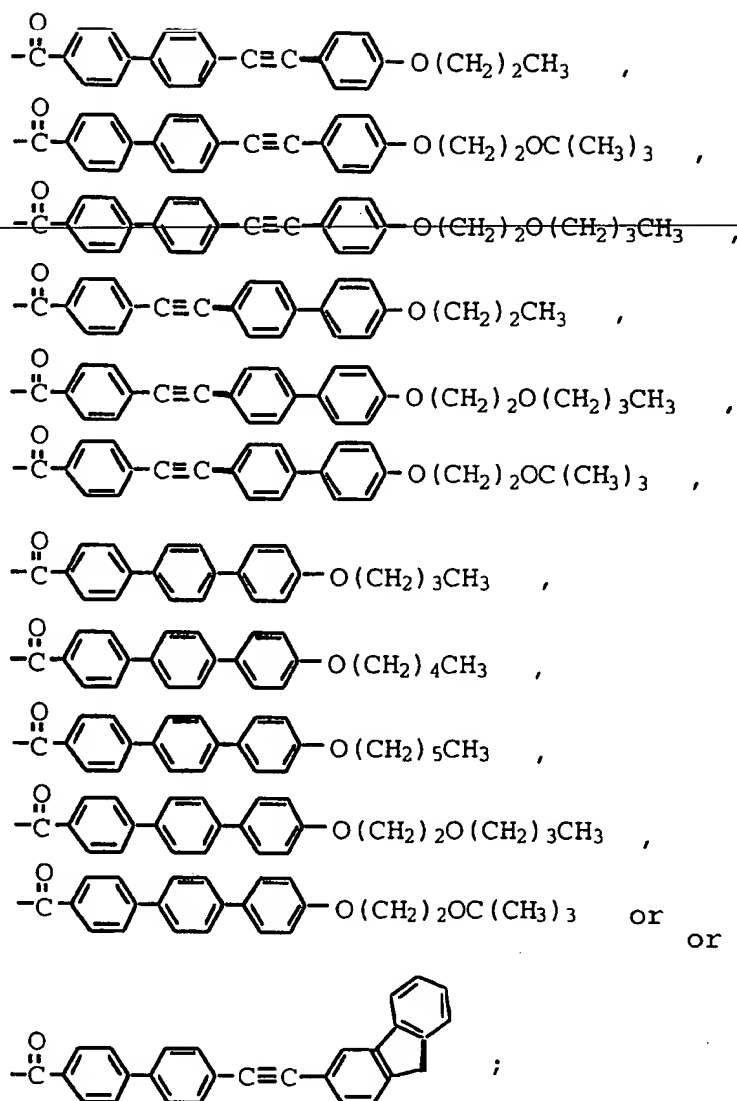
R¹ is phenyl, or a compound of the formula



20 where R^{1a} is hydrogen, halo, C₁-C₆ alkyl or C₁-C₆ alkoxy;

R₂ is an acyl group of the formula:

- 73 -



or a pharmaceutically acceptable salt thereof.

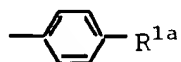
5

12. A process according to claim 11 for preparing a compound of formula IIA where:

R is methyl;

R¹ is phenyl or a compound of the formula

10



where R^{1a} is halo or hydrogen;

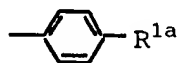
or a pharmaceutically acceptable salt thereof.

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13. A process according to claim 12 for preparing a compound of formula IIA where:

R¹ is phenyl or a compound of the formula

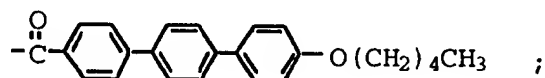
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where R^{1a} is bromo or hydrogen;
or a pharmaceutically acceptable salt thereof.

10 14. A process according to claim 13 for preparing a compound of formula IIA where:

R₂ is



or a pharmaceutically acceptable salt thereof.

15

15. A process according to claim 10 which comprises reacting a compound of formula I where R is methyl and R' is phenyl or 4-bromophenyl.

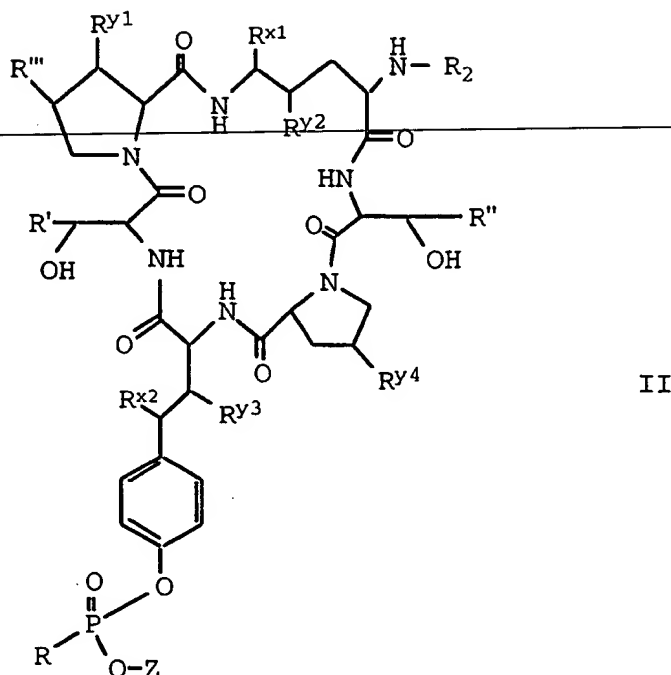
20 16. A process according to claim 10 wherein the compound of formula I is a mixture of syn and anti diastereomers.

25 17. A process according to claim 15 wherein the compound of formula I is a mixture of syn and anti diastereomers.

30 18. A process according to claim 15 wherein the compound of formula I is the substantially purified syn or anti diastereomer.

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19. A process for converting a compound of formula
II:



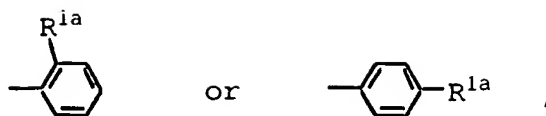
wherein:

- 5 R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;
 R'' and R''' are independently methyl or hydrogen;
 R^{x1}, R^{x2}, R^{y1}, R^{y2}, R^{y3}, and R^{y4} are independently
 hydroxy or hydrogen;
 R is C₁-C₆ alkyl, phenyl or benzyl;
 10 Z is $-\text{CH}_2-\text{R}^1$;
 R¹ is phenyl, naphthyl, cyclohexyl or a compound of
 the formula



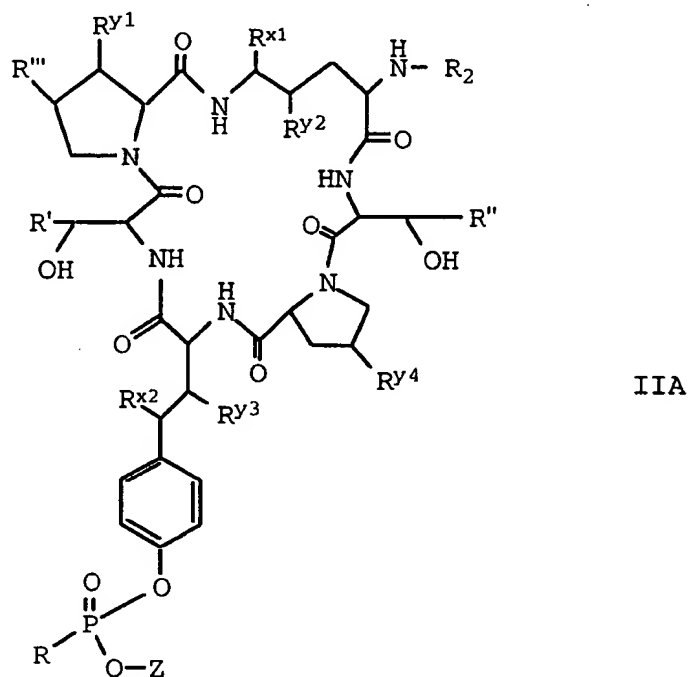
- 15 where R^{1a} is hydrogen, halo, trifluoromethyl, C₁-C₆ alkyl,
 C₁-C₆ alkoxy, hydroxy, cyano, nitro, protected amino,
 phenyl, benzyl or benzyloxy;
 R₂ is acyl;
 with the proviso that when R¹ is

- 76 -



then R^{1a} cannot be hydroxy, $\text{C}_1\text{-C}_6$ alkoxy or benzyloxy;
~~or a pharmaceutically acceptable salt thereof;~~
 to a compound of formula IIA:

5



where:

R' , R'' , R''' , R^{x1} , R^{x2} , R^{y1} , R^{y2} , R^{y3} , R^{y4} , R and R_2 are as defined above; and

10

Z is hydrogen,

which comprises

1) hydrogenating the compound of formula II by

a) exposure to hydrogen gas in the presence of a catalyst and a base; or

15

b) reaction with an alkali metal in liquid ammonia; and

2) optionally forming a pharmaceutically acceptable salt.

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20. The process according to claim 19 where the compound of formula II is hydrogenated by exposure to hydrogen gas where the catalyst is palladium or platinum on a solid support and the base triethylamine, N-methyl morpholine, pyridine, diisopropylethylamine.

21. The process according to claim 19 where the catalyst is palladium-on-carbon and the base is triethylamine.

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16195

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/12; C07F 9/40; C07K 1/113, 7/56

US CL :514/7, 11; 530/317, 345; 558/152

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/7, 9, 11; 530/317, 345; 558/152

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2,632,768 A (COOVER, Jr. et al.) 24 March 1953 (24/03/53), column 1, lines 48-55.	1-4
X	US 5,359,115 A (CAMPBELL et al.) 25 October 1994 (25/10/94), Figure 5, column 17, lines 51-54.	1
A, P	US 5,786,325 A (BORROMEIO et al.) 28 July 1998 (28/07/98), column 1, line 44 - column 2, line 44.	5-21
A	US 5,646,111 A (BORROMEIO et al.) 08 July 1997 (08/07/97), column 1, line 44 - column 4, line 15, Table 2.	5-21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

23 SEPTEMBER 1998

Date of mailing of the international search report

30 OCT 1998

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BALKOVEC et al. Synthesis, Stability, and Biological Evaluation of Water-Soluble Prodrugs of a New Echinocandin Lipopeptide. Discovery of a Potential Clinical Agent for the Treatment of Systemic Candidiasis and Pneumocystis carinii Pneumonia (PCP). Journal of Medicinal Chemistry. 1992, Volume 35, Number 1, pages 194-198, especially Table I, page 196, column 2, formula 4.	5-21

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International application No.
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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CHEMICAL ABSTRACTS, DIALOG:

search terms: phosphonic, phosphonate, pyrophosphonic, prodrug, echinocandin, pneumocandin, structures of formulas I and II